Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: F

Diseases

Cancer, Ophthalmology & Pediatric

Erlotinib Induced Fatal

Polyarteritis Nodosa Renal Crisis

Highlights

Estimation of New Drug

Waldenstrom's Macroglobulinema

Discovering Thoughts, Inventing Future

VOLUME 16 ISSUE 5 VERSION 1.0

© 2001-2016 by Global Journal of Medical Research, USA

Global Journal of Medical Research: F
Diseases
Cancer, Ophthalmology & Pediatric

Global Journal of Medical Research: F
Diseases
Cancer, Ophthalmology & Pediatric

Volume 16 Issue 5 (Ver. 1.0)

Open Association of Research Society

© Global Journal of Medical Research. 2016.

All rights reserved.

This is a special issue published in version 1.0 of "Global Journal of Medical Research." By Global Journals Inc.

All articles are open access articles distributed under "Global Journal of Medical Research"

Reading License, which permits restricted use. Entire contents are copyright by of "Global Journal of Medical Research" unless otherwise noted on specific articles.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission.

The opinions and statements made in this book are those of the authors concerned. Ultraculture has not verified and neither confirms nor denies any of the foregoing and no warranty or fitness is implied.

Engage with the contents herein at your own risk.

The use of this journal, and the terms and conditions for our providing information, is governed by our Disclaimer, Terms and Conditions and Privacy Policy given on our website http://globaljournals.us/terms-and-condition/menu-id-1463/

By referring / using / reading / any type of association / referencing this journal, this signifies and you acknowledge that you have read them and that you accept and will be bound by the terms thereof.

All information, journals, this journal, activities undertaken, materials, services and our website, terms and conditions, privacy policy, and this journal is subject to change anytime without any prior notice.

Incorporation No.: 0423089
License No.: 42125/022010/1186
Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

Global Journals Inc.

*(A Delaware USA Incorporation with "Good Standing"; **Reg. Number: 0423089**)*

Sponsors: Open Association of Research Society
Open Scientific Standards

Publisher's Headquarters office

Global Journals® Headquarters
945th Concord Streets,
Framingham Massachusetts Pin: 01701,
United States of America
USA Toll Free: +001-888-839-7392
USA Toll Free Fax: +001-888-839-7392

Offset Typesetting

Global Journals Incorporated
2nd, Lansdowne, Lansdowne Rd., Croydon-Surrey,
Pin: CR9 2ER, United Kingdom

Packaging & Continental Dispatching

Global Journals
E-3130 Sudama Nagar, Near Gopur Square,
Indore, M.P., Pin: 452009, India

Find a correspondence nodal officer near you

To find nodal officer of your country, please email us at *local@globaljournals.org*

eContacts

Press Inquiries: *press@globaljournals.org*
Investor Inquiries: *investors@globaljournals.org*
Technical Support: *technology@globaljournals.org*
Media & Releases: *media@globaljournals.org*

Pricing (Including by Air Parcel Charges):

For Authors:
22 USD (B/W) & 50 USD (Color)
Yearly Subscription (Personal & Institutional):
200 USD (B/W) & 250 USD (Color)

Global Journals Constitutional Editorial Board

~Integrated~

Dr. Charles A. Rarick

Ph.D.

Professor of International Business

College of Business

Purdue University Northwest

Hammond, Indiana USA

Dr. Osman Balci, Professor

Department of Computer Science

Virginia Tech, Virginia University

Ph.D. and M.S. Syracuse University, Syracuse, New York

M.S. and B.S. Bogazici University, Istanbul, Turkey

Web: manta.cs.vt.edu/balci

Dr. A. Heidari

Ph.D, D.Sc, Faculty of Chemistry

California South University (CSU),

United Stated

Dr. Miklas Scholz

B.Eng. (equiv), PgC, MSc, Ph.D, CWEM, C.Env., CSci, C.Eng.

Nigeria Health, Wellness and Fitness

University of Lund

Dr. Maria Gullo

Ph.D, Food Science and Technology

University of Catania

Department of Agricultural and Food Sciences

University of Modena and Reggio Emilia, Italy

Dr. Qiang Wu

Ph.D University of Technology, Sydney

Department of Mathematics,

Physics and Electrical Engineering

Northumbria University

Dr. Bingyun Li

Ph.D Fellow, IAES

Guest Researcher, NIOSH, CDC, Morgantown, WV

Institute of Nano and Biotechnologies

West Virginia University, US

Dr. Audeh Ahmad Ahmad

Amman Arab University For Higher Education

Ph.D, Accounting-Ais

Faculty of Business Administration

Alalbyt University, Jordan, Amman

Dr. Lucian Baia

Ph.D Julius-Maximilians University Würzburg, Germany

Associate professor

Department of Condensed Matter Physics and

Advanced Technologies, Babes-Bolyai University, Romania

Dr. Sahraoui Chaieb

PhD Physics and Chemical Physics

M.S. Theoretical Physics

B.S. Physics, École Normale Supérieure, Paris

Associate Professor, Bioscience

King Abdullah University of Science and Technology

Dr. Houfa Shen

Ph.D Manufacturing Engineering,

Mechanical Engineering, Structural Engineering

Department of Mechanical Engineering

Tsinghua University, China

Dr. Arshak Poghossian

Ph.D Solid-State Physics

Leningrad Electrotechnic Institute, Russia

Institute of Nano and Biotechnologies

Aachen University of Applied Sciences, Germany

Dr. A. Stegou-Sagia

Ph.D Mechanical Engineering, Environmental
Engineering School of Mechanical Engineering
National Technical University of Athens

Dr. Adel Al Jumaily

Ph.D Electrical Engineering (AI)
Faculty of Engineering and IT
University of Technology, Sydney

Giuseppe A Provenzano

Irrigation and Water Management, Soil Science,
Water Science Hydraulic Engineering
Dept. of Agricultural and Forest Sciences
Universita di Palermo, Italy

Kitipong Jaojaruek

B. Eng, M. Eng D. Eng (Energy Technology, Asian Institute of Technology).
Kasetsart University Kamphaeng Saen (KPS) Campus
Energy Research Laboratory of Mechanical Engineering

Dr. Ciprian LĂPUȘAN

Ph. D in Mechanical Engineering
Technical University of Cluj-Napoca
Cluj-Napoca (Romania)

Dr. Mauro Lenzi

Ph.D, Biological Science, Pisa University, Italy
Lagoon Ecology and Aquaculture Laboratory
Orbetello Pesca Lagunare Company

Dr. Haijian Shi

Ph.D Civil Engineering Structural Engineering
Oakland, CA, United States

Dr. Omid Gohardani

M.Sc. (Computer Science), FICCT, U.S.A.
Email: yogita@computerresearch.org

Dr. Yogita Bajpai

Ph.D Senior Aerospace/Mechanical/
Aeronautical Engineering professional
M.Sc. Mechanical Engineering
M.Sc. Aeronautical Engineering
B.Sc. Vehicle Engineering
Orange County, California, USA

Dr. Yap Yee Jiun

B.Sc.(Manchester), Ph.D.(Brunel), M.Inst.P.(UK)
Institute of Mathematical Sciences,
University of Malaya,
Kuala Lumpur, Malaysia

Dr. Abdurrahman Arslanyilmaz

Computer Science & Information Systems Department
Youngstown State University
Ph.D., Texas A&M University
University of Missouri, Columbia
Gazi University, Turkey
Web:cis.ysu.edu/~aarslanyilmaz/professional_web

Dr. Thomas Wischgoll

Computer Science and Engineering,
Wright State University, Dayton, Ohio
B.S., M.S., Ph.D.
(University of Kaiserslautern)
Web:avida.cs.wright.edu/personal/wischgol/index_eng.html

Dr. Chao Wang

Ph.D. in Computational Mechanics
Rosharon, TX, USA

Dr. Baziotis Ioannis

Ph.D. in Petrology-Geochemistry-Mineralogy
Lipson, Athens, Greece

Dr. Xiaohong He

Professor of International Business

University of Quinnipiac

BS, Jilin Institute of Technology; MA, MS, Ph.D,

(University of Texas-Dallas)

Web: quinnipiac.edu/x1606.xml

Dr. T. David A. Forbes

Associate Professor and Range Nutritionist

Ph.D Edinburgh University - Animal Nutrition

M.S. Aberdeen University - Animal Nutrition

B.A. University of Dublin- Zoology.

Web: essm.tamu.edu/people-info/faculty/forbes-david

Dr. Burcin Becerik-Gerber

University of Southern Californi

Ph.D in Civil Engineering

DDes from Harvard University

M.S. from University of California, Berkeley

M.S. from Istanbul Technical University

Web: i-lab.usc.edu

Dr. Bassey Benjamin Esu

B.Sc. Marketing; MBA Marketing; Ph.D Marketing

Lecturer, Department of Marketing, University of Calabar

Tourism Consultant, Cross River State Tourism Development Department

Co-rdinator , Sustainable Tourism Initiative, Calabar, Nigeria

Dr. Söhnke M. Bartram

Department of Accounting and Finance

Lancaster University Management School

Ph.D. (WHU Koblenz)

MBA/BBA (University of Saarbrücken)

Web: lancs.ac.uk/staff/bartras1/

Dr. Maciej Gucma

Asistant Professor,

Maritime University of Szczecin Szczecin, Poland

Ph.D. Eng. Master Mariner

Web: www.mendeley.com/profiles/maciej-gucma/

Dr. Söhnke M. Bartram

Ph.D, (IT) in Faculty of Engg. & Tech.

Professor & Head,

Dept. of ISE at NMAM Institute of Technology

Dr. Shun-Chung Lee

Department of Resources Engineering,

National Cheng Kung University, Taiwan

Dr. Balasubramani R

Department of Accounting and Finance

Lancaster University Management School

Ph.D. (WHU Koblenz)

MBA/BBA (University of Saarbrücken)

Web: lancs.ac.uk/staff/bartras1/

Dr. Fotini Labropulu

Mathematics - Luther College, University of Regina

Ph.D, M.Sc. in Mathematics

B.A. (Honours) in Mathematics, University of Windsor

Web: luthercollege.edu/Default.aspx

M. Meguellati

Department of Electronics,

University of Batna, Batna 05000, Algeria

Dr. Vesna Stanković Pejnović

Ph. D. Philospohy , Zagreb, Croatia

Rusveltova, Skopje, Macedonia

Dr. Miguel Angel Ariño

Professor of Decision Sciences

IESE Business School

Barcelona, Spain (Universidad de Navarra)

CEIBS (China Europe International Business School).

Beijing, Shanghai and Shenzhen

Ph.D. in Mathematics, University of Barcelona

BA in Mathematics (Licenciatura)

University of Barcelona

Web:web.iese.edu/MAArino/overview.axd

Dr. Carlos García Pont

Associate Professor of Marketing

IESE Business School, University of Navarra

Doctor of Philosophy (Management),

Massachussetts Institute of Technology (MIT)

Master in Business Administration, IESE,

University of Navarra

Degree in Industrial Engineering,

Universitat Politècnica de Catalunya

Web: iese.edu/aplicaciones/faculty/facultyDetail.asp

Dr. Philip G. Moscoso

Technology and Operations Management

IESE Business School, University of Navarra

Ph.D in Industrial Engineering and Management,

ETH Zurich , M.Sc. in Chemical Engineering,

ETH Zurich Link: Philip G. Moscoso personal webpage

Dr. Sanjay Dixit, M.D.

Director, EP Laboratories, Philadelphia VA Medical Center

Cardiovascular Medicine - Cardiac Arrhythmia

University of Penn School of Medicine

Web: pennmedicine.org/wagform/MainPage.aspx?

Dr. Mihaly Mezei

Associate Professor

Department of Structural and Chemical Biology

Mount Sinai School of Medical Center

Ph.D., Etvs Lornd University, Postdoctoral Training,

New York University, MSSM home:

https://www.mountsinai.org/Find%20A%20Faculty/profile.do?id=0000072500001497192632

Lab home - software,

publications: https://inka.mssm.edu/~mezei

Department: https://atlas.physbio.mssm.edu

Dr. Pina C. Sanelli

Associate Professor of Radiology

Associate Professor of Public Health

Weill Cornell Medical College

Associate Attending Radiologist

NewYork-Presbyterian Hospital

MRI, MRA, CT, and CTA

Neuroradiology and Diagnostic Radiology

M.D., State University of New York at Buffalo,

School of Medicine and Biomedical Sciences

Web: weillcornell.org/pinasanelli/

Dr. Vivek Dubey (HON.)

MS (Industrial Engineering),

MS (Mechanical Engineering)

University of Wisconsin

FICCT

Editor-in-Chief, USA

Er. Suyog Dixit

(M.Tech), BE (HONS. in CSE), FICCT

SAP Certified Consultant

CEO at IOSRD, GAOR OSS

Technical Dean, Global Journals Inc.(US)

Website: www.suyogdixit.com

Email: suyog@suyogdixit.com

Er. Pritesh Rajvaidya

Computer Science Department

California State University

BE (Computer Science), FICCT

Technical Dean, USA

Email: pritesh@computerresearch.org,

deanusa@globaljournals.org

Jixin Zhong

Department of Medicine,

Affiliated Hospital of Guangdong Medical College,

Zhanjiang, China Davis Heart and Lung Research Institute,

The Ohio State University, Columbus, OH 43210, USA

Dr. Apostolos Ch. Zarros

DM, Degree (Ptychio) holder in Medicine,

National and Kapodistrian University of Athens

MRes, Master of Research in Molecular Functions in Disease,

University of Glasgow

FRNS, Fellow, Royal Numismatic Society

Member, European Society for Neurochemistry

Member, Royal Institute of Philosophy

Scotland, United Kingdom

Dr. Wen-Yih Sun

Professor of Earth and Atmospheric Sciences

Purdue University, Director

National Center for Typhoon and Flooding Research, Taiwan

University Chair Professor

Department of Atmospheric Sciences,

National Central University, Chung-Li, Taiwan

University Chair Professor

Institute of Environmental Engineering,

National Chiao Tung University, Hsin-chu, Taiwan.

Ph.D., MS The University of Chicago, Geophysical Sciences

BS National Taiwan University, Atmospheric Sciences

Web: event.nchc.org.tw/2009

Dr. Han-Xiang Deng

MD., Ph.D

Associate Professor and Research Department

Division of Neuromuscular Medicine

Davee Department of Neurology and Clinical Neurosciences

Northwestern University Feinberg School of Medicine

Web:neurology.northwestern.edu/faculty/deng.html

Dr. Michael R. Rudnick

M.D., FACP

Associate Professor of Medicine

Chief, Renal Electrolyte and Hypertension Division (PMC)

Penn Medicine, University of Pennsylvania

Presbyterian Medical Center, Philadelphia

Nephrology and Internal Medicine

Certified by the American Board of Internal Medicine

Web: uphs.upenn.edu/

Dr. Roberto Sanchez

Associate Professor

Department of Structural and Chemical Biology

Mount Sinai School of Medicine

Ph.D., The Rockefeller University

Web: mountsinai.org/

Dr. Aziz M. Barbar, Ph.D.

IEEE Senior Member

Chairperson, Department of Computer Science

AUST - American University of Science & Technology

Alfred Naccash Avenue - Ashrafieh

Dr. Minghua He

Department of Civil Engineering
Tsinghua University
Beijing, 100084, China

Anis Bey

Dept. of Comput. Sci.,
Badji Mokhtar-Annaba Univ.,
Annaba, Algeria

Chutisant Kerdvibulvech

Dept. of Inf.& Commun. Technol.,
Rangsit University, Pathum Thani, Thailand
Chulalongkorn University, Thailand
Keio University, Tokyo, Japan

Dr. Wael Abdullah

Elhelece Lecturer of Chemistry,
Faculty of science, Gazan Univeristy,
KSA. Ph. D. in Inorganic Chemistry,
Faculty of Science, Tanta University, Egypt

Yaping Ren

School of Statistics and Mathematics
Yunnan University of Finance and Economics
Kunming 650221, China

Ye Tian

The Pennsylvania State University
121 Electrical Engineering East
University Park, PA 16802, USA

Dr. Diego González-Aguilera

Ph.D. Dep. Cartographic and Land Engineering,
University of Salamanca, Ávila, Spain

Dr. Hai-Linh Tran

PhD in Biological Engineering
Department of Biological Engineering
College of Engineering Inha University, Incheon, Korea

Dr. Tao Yang

Ph.D, Ohio State University
M.S. Kansas State University
B.E. Zhejiang University

Dr. Feng Feng

Boston University
Microbiology, 72 East Concord Street R702
Duke University
United States of America

Shengbing Deng

Departamento de Ingeniería Matemática,
Universidad de Chile.
Facultad de Ciencias Físicas y Matemáticas.
Blanco Encalada 2120, piso 4.
Casilla 170-3. Correo 3. - Santiago, Chile

Claudio Cuevas

Department of Mathematics
Universidade Federal de Pernambuco
Recife PE Brazil

Dr. Alis Puteh

Ph.D. (Edu.Policy) UUM
Sintok, Kedah, Malaysia
M.Ed (Curr. & Inst.), University of Houston, USA

Dr. R.K. Dixit(HON.)

M.Sc., Ph.D., FICCT Chief Author, India
Email: authorind@globaljournals.org

Dr. Dodi Irawanto

PhD, M.Com, B.Econ Hons.
Department of Management,
Faculty of Economics and Business, Brawijaya University
Malang, Indonesia

Ivona Vrdoljak Raguz

University of Dubrovnik, Head,
Department of Economics and Business Economics,
Croatia

Dr. Prof Adrian Armstrong

BSc Geography, LSE, 1970
PhD Geography (Geomorphology)
Kings College London 1980
Ordained Priest, Church of England 1988
Taunton, Somerset, United Kingdom

Thierry FEUILLET

Géolittomer – LETG UMR 6554 CNRS
(Université de Nantes)
Institut de Géographie et d'Aménagement
Régional de l'Université de Nantes.
Chemin de la Censive du Tertre – BP, Rodez

Dr. Yongbing Jiao

Ph.D. of Marketing
School of Economics & Management
Ningbo University of Technology
Zhejiang Province, P. R. China

Cosimo Magazzino

Roma Tre University
Rome, 00145, Italy

Dr. Shaoping Xiao

BS, MS, Ph.D Mechanical Engineering,
Northwestern University
The University of Iowa
Department of Mechanical and Industrial Engineering
Center for Computer-Aided Design

Dr. Alex W. Dawotola

Hydraulic Engineering Section,
Delft University of Technology,
Stevinweg, Delft, Netherlands

Dr. Luisa dall'Acqua

PhD in Sociology (Decisional Risk sector),
Master MU2, College Teacher in Philosophy (Italy),
Edu-Research Group, Zürich/Lugano

Xianghong Qi

University of Tennessee
Oak Ridge National Laboratory
Center for Molecular Biophysics
Oak Ridge National Laboratory
Knoxville, TN 37922, United States

Gerard G. Dumancas

Postdoctoral Research Fellow,
Arthritis and Clinical Immunology Research Program,
Oklahoma Medical Research Foundation
Oklahoma City, OK
United States

Vladimir Burtman

Research Scientist
The University of Utah, Geophysics
Frederick Albert Sutton Building, 115 S 1460 E Room 383
Salt Lake City, UT 84112, USA

Jalal Kafashan

Mechanical Engineering, Division of Mechatronics
KU Leuven, BELGIUM

Zhibin Lin

Center for Infrastructure Engineering Studies
Missouri University of Science and Technology
ERL, 500 W. 16th St. Rolla,
Missouri 65409, USA

Dr. Lzzet Yavuz

MSc, PhD, D Ped Dent.

Associate Professor,

Pediatric Dentistry Faculty of Dentistry,

University of Dicle, Diyarbakir, Turkey

Prof. Dr. Eman M. Gouda

Biochemistry Department,

Faculty of Veterinary Medicine, Cairo University,

Giza, Egypt

Della Ata

BS in Biological Sciences

MA in Regional Economics

Hospital Pharmacy

Pharmacy Technician Educator

Dr. Muhammad Hassan Raza, PhD

Engineering Mathematics

Internetworking Engineering, Dalhousie University,

Canada

Dr. Asunción López-Varela

BA, MA (Hons), Ph.D (Hons)

Facultad de Filología.

Universidad Complutense Madrid

29040 Madrid, Spain

Dr. Bondage Devanand Dhondiram

Ph.D

No. 8, Alley 2, Lane 9, Hongdao station,

Xizhi district, New Taipei city 221, Taiwan (ROC)

Dr. Latifa Oubedda

National School of Applied Sciences,

University Ibn Zohr, Agadir, Morocco

Lotissement Elkhier N°66

Bettana Salé Maroc

Dr. Belen Riverio, PhD

School of Industrial Enigneering

University of Vigo

Spain

Contents of the Issue

i. Copyright Notice
ii. Editorial Board Members
iii. Chief Author and Dean
iv. Contents of the Issue

1. Polyarteritis Nodosa Renal Crisis with Malignant Hypertension. *1-3*
2. Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials. *5-16*
3. Acute Kidney Injury and Massive Proteinuria Secondary to Epstein - Barr Virus - Associated Nephrotic Syndrome. *17-18*
4. Childhood Hypocalcemia: The Aetiological Pattern. *19-21*
5. Erlotinib Induced Fatal Interstitial Lung Disease: An Underreported Toxicity. *23-28*
6. The Effect of Green Leafy Vegetable Intake on the Incidence of Urothelial Cancers: A Meta-Analysis. *29-36*
7. Waldenstrom's Macroglobulinema Presenting as Syncope. *37-38*
8. Central Neurogenic Hyperventilation with Acute Respiratory Alkalosis, Transient Lactic Acidosis and Tachycardia Following Endoscopic Third Ventriculostomy in a Child- A Case Report. *39-43*
9. Describe the Various Types of Neuropathy Observed in Patients with Diabetes. *45-48*
10. Staphylococcus Associated Glomerulonephritis with IgA Mesangial Deposition. *49-52*

v. Fellows
vi. Auxiliary Memberships
vii. Process of Submission of Research Paper
viii. Preferred Author Guidelines
ix. Index

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Polyarteritis Nodosa Renal Crisis with Malignant Hypertension

By Awad Magbri, MD
Partners in Nephrology and Endocrinology, United States

Abstract- A case of 28 years female with no significant past medical history presented with malignant hypertension. She was found to have Polyarteritis nodosa involving the kidney on angiography. She was treated successfully with steroids and cytotoxic drugs and made uneventful recovery. Her kidney function remained stable and her BP was controlled on Po medications. Even though she was negative for hepatitis B infection, the association was strongly confirmed in about 10% of patients. PAN should be suspected in any patients with multisystem involvement with hypertension and minimal findings in urinalysis. Polyneuropathy and high ESR are also red flags for PAN.

GJMR-F Classification: NLMC Code: WG518

Strictly as per the compliance and regulations of:

© 2016. Awad Magbri, MD. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/ 3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Polyarteritis Nodosa Renal Crisis with Malignant Hypertension

Awad Magbri, MD

Abstract- A case of 28 years female with no significant past medical history presented with malignant hypertension. She was found to have Polyarteritis nodosa involving the kidney on angiography. She was treated successfully with steroids and cytotoxic drugs and made uneventful recovery. Her kidney function remained stable and her BP was controlled on Po medications. Even though she was negative for hepatitis B infection, the association was strongly confirmed in about 10% of patients. PAN should be suspected in any patients with multisystem involvement with hypertension and minimal findings in urinalysis. Polyneuropathy and high ESR are also red flags for PAN.

I. Case History

28 years Caucasian female without any significant past medical history was admitted to the hospital for severe frontal headache of one month duration. Family history is significant for hypertension in her father and granduncle. In the week proceeding presentation to the hospital, she had taken 6-8 (60 mg) pseudoephedrine tablets for head cold. Her blood pressure was 248/177 mmHg. Her eye examination showed retinal hemorrhage, cotton wool spots, and papilledema. Otherwise, her physical examination was unremarkable. Her renal ultrasound revealed bilateral symmetrical kidneys of 11.2 cm size, with mild medical-renal parenchymal disease.

Captopril renogram was suggestive of bilateral renal artery stenosis which was ruled out by angiography. Routine laboratory was within normal limits with serum creatinine 1 mg/dl, and 24-hour creatinine clearance of 112 ml/min.

Tests for hepatitis B, C, and RF, ANA, anti-DNA and ANCA were negative. Her ESR was 10 mm/hr. Renin level at 8 am in the supine position was 26 μU/ml (normal <5). The 24-hour urine catecholamine were collected in the second day of admission were found to be within normal limits.

ECG showed LVH, and CXR and CT of head were normal.

A diagnosis was made by angiography of the kidneys and the patient was treated with

- High dose steroids (1000 mg methyl-prednisone IV daily for three consecutive days).
- Prednisone 1 mg/kg/day PO x 3 weeks, the prednisone was then tapered slowly.
- Cyclophosphamide 0.6 g/M^2 monthly IV for 6 months.
- Hypertension became controlled, average BP 132/80 mmHg within 2-3 weeks.
- The patient was initially stabilized with IV nitro-prusside and Labetalol and then switched later to oral regimen consists of Lisinopril 20 mg/day, Hydrochlorothiazide 12.5 mg daily, and Labetalol 400 mg three times daily.
- Her renal function remained stable throughout the treatment course.

II. Discussion

Poly- arteritis nodosa (PAN) is a systemic vasculitis characterized by necrotizing inflammatory lesions affecting predominantly medium and small muscular arteries, resulting in micro-aneurysmal formation, thrombosis, rupture with hemorrhage, and organ infarction (1-3).

PAN is a rare disease with an incidence of 4.6 cases/million in England to 77 cases/million in hyper-endemic areas for hepatitis B. PAN affected both sexes and has been diagnosed in all racial groups.

The etiology of PAN remained unknown and hepatitis B, hepatitis C, and Hairy cell leukemia are associated with some cases of PAN (4-7). The current incidence is $<10\%$ because of hepatitis B vaccination.

In contrast to microscopic polyangitis (MPA), PAN is not associated with anti-nuclear cytoplasmic antibodies (ANCA) and does not affect the glomeruli. PAN is acute multisystem disease with relatively short prodrome. For unknown reasons PAN spars the lungs.

Skin manifestation of PAN may include tender erythematous nodules, purpura, livedo reticularis, ulcers, and vesicular eruption (8-10). The erythematous nodule resembles erythema nodosum, but biopsy of these nodules reveals necrotizing vasculitis in the walls of the medium sized arteries.

Renal involvement by PAN frequently, leads to renal insufficiency and hypertension. Incomplete luminal narrowing of the inflamed arteries leads to glomerular ischemia but no inflammation or necrosis. Renal ischemia usually leads to activation of the renin-angiotensin system (2). Thus, the urinalysis, when abnormal, shows only sub-nephrotic and minimal proteinuria and sometimes hematuria, but red cell casts (indicative of glomerulitis are usually absent (1,11).

Author: *Dialysis Access Center of Pittsburgh, PA.*
e-mail: elmagbri@hotmail.com

© 2016 Global Journals Inc. (US)

Neurological disease of PAN includes asymmetric polyneuropathy affecting radial, ulnar, peroneal etc. These neuropathies are usually mixed motor and sensory occurring in up to 70% of patients (8,12-14). Central nervous system is involved in 5-10% of patients with PAN (8,15-17).

Gastrointestinal disease is an early symptom in patients with PAN including mesenteric arteritis (18), Weight loss, malabsorption, bowel infarction with perforation may also occurs (19).

Muscle weakness and myalgia with elevated CPK may trigger suspicion of inflammatory myopathy. Muscle biopsy has an approximately 50% sensitivity for the diagnosis of PAN (20,21). Orchitis with testicular tenderness (22), eye involvement with ischemic retinopathy (23,24), and splenic infraction may occurs.

The diagnosis of PAN may be difficult due to non-specific signs and symptoms, multi-system involvement and the rarity of the disease. However, the sedimentation rate is elevated in about 90% of patients. The clinical manifestations of PAN are illustrated in table-1.

Table-1: Clinical manifestation of PAN

Clinical Feature	Percentage
Fever, malaise, weight loss	70%
Pain and peripheral neuropathy	70%
Myalgia	30-73%
Arthralgia and polyarthritis	20-50%
Abdominal pain	34%
Depression	8%
Renal involvement (CKD, HTN), activation of RAAS may lead to malignant HTN	25-70%

Tissue biopsy of the affected organs and or angiography may clinch the diagnosis. The palpable purpuric lesions seen in PAN are identical to vasculitis associated with small vessels disease (e.g IgA vasculitis, ANCA- associated vasculitis, and mixed cryoglobulinemia) (25).

Due to sampling error the diagnosis of PAN may be missed on renal biopsy, but renal angiography may be diagnostic with specificity of 95%.

PAN has a 5 year survival of <10% if untreated. Treatment of PAN consisted of high doses steroids and intra-venous pulse cyclophosphamide. This treatment achieves a 5-year survival of 82%.

- 115 patients with PAN, (4.2%) had severe hypertension during the 1 year of presentation of the disease. Renal insufficiency, gastrointestinal disease, and positive hepatitis B were present in the majority of these patients (4).
- Many patients with PAN reported in the literature had isolated renal involvement with severe hypertension (8).

III. Conclusion

PAN should be suspected in any patients with multisystem involvement with hypertension and minimal findings in urinalysis. Polyneuropathy and high ESR are also red flags for PAN. PAN is rare disease especially after wide spread vaccination for hepatitis B. Steroids and cytotoxic medications remain the foundation of treatment of PAN.

References Références Referencias

1. Sato O, Cohn DL. Polyarteritis and microscopic polyangitis. In: Rheumatology, Kippel JH, Dieppe PA (Eds), Mosby, St Louis 2003
2. Stockigt JR, Topliss DJ, Hewett MJ. High-renin hypertension in necrotizing vasculitis. N Engl J Med 1979; 300: 1218
3. Ng WF, Chow LT, Lam PW. Localized Polyarteritis nodosa of the breast- report of two cases and review of the literature. Histopathology 1993; 23: 535.
4. Guillevin L, Mahr A, Callard P, et al. Hepatitis B virus-associated Polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. Medicine (Baltimore) 2005; 84: 313
5. Ramos-Casals M, Munoz S, Medina F, et al. Systemic autoimmune diseases in patients with hepatitis C virus infection: characterization of 1020 cases (The HISPAMEC Registry). J Rheumatol 2009; 36: 1442.
6. Hasler P, Kistler H, Gerber H. Vasculitides in hairy cell leukemia. Semin Arthitis Rheum 1995; 25: 134.
7. Carpenter MT, West SG. Polyarteritis nodosa in hairy cell leukemia: treatment with interferon-alpha. J Rheumatol 1994; 21: 1150.
8. Pagnoux C, Seror R, Henegar C, et al. Clinical features and outcomes in 348 patients with Polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study group database. Arthritis Rheum 2010; 62: 616.
9. Gibson LE, Su WP. Cutaneous vasculitis. Rheum Dis Clin North AM 1995; 21: 1097.
10. Karlsberg PL, Lee WM, Casey DL, et al. Cutaneous vasculitis and rheumatoid factor positivity as presenting signs of hepatitis C virus-induced mixed cryoglobulinemia. Arch Dermatol 1995; 131: 1119.
11. Balow JE. Renal vasculitis. Kidney Int 1985; 27: 954.
12. Ohkoshi N, Mizusawa H, Oguni E, et al. Sural nerve biopsy in vasculitic neuropathies: morphometric analysis of the caliber of invoved vessels. J Med 1996; 27: 153.
13. Tervaert JW, Kallenberg C. Neurologic manifestations of systemic vasculitides. Rheum Dis Clin North AM 1993; 19: 913.
14. Moore PM. Neurological manifestation of vasculitis: update on immunopathogenic mechanisms and

© 2016 Global Journals Inc. (US)

clinical features. Ann Neurol 1995: 37 suppl (1): S131.
15. Provenzale JM, Allen NB. Neuroradiologic findings in Polyarteritis nodosa. AJNR AM J Neuroradiol 1996; 17: 1119.
16. Cohen RD, Conn DL, Ilstrup DM. Clinical features, prognosis, and response to treatment in Polyarteritis. Mayo Clin Proc 1980; 55: 146.
17. Reichart MD, Bogousslavsky J, Janzer RC. Early lacunar strokes complicating Polyarteritis nodosa: thrombotic microangiopathy. Neurology 2000; 54: 883.
18. Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with Polyarteritis nodosa, microscopic polyangitis, Wegner granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. Medicine (Baltimore) 2005; 84: 115.
19. Zizic TM, Classen JN, Stevens MB. Acute abdominal complications of systemic lupus erythematosis and Polyarteritis nodosa. Am J Med 1982; 73: 525.
20. Plumley SG, Rubio R, Alasfar S, Jasin HE. Polyarteritis nodosa presenting as polymyositis. Semin Arthitis Rheum 2002; 31: 377.
21. Fort JG, Griffin R, Tahmoush A, Abruzzo JL. Muscle involvement in Polyarteritis nodosa: report of a patient presenting clinically as polymyositis and review of the literature. J Rheumatol 1994; 21: 945.
22. Teichman JM, Mattrey RF, Demby AM, Schmidt JD. Polyarteritis nodosa presenting as acute Orchitis: a case report and review of the literature. J Urol 1993; 149: 1139.
23. Akova YA, Jabbur NS, Foster CS. Ocular presentation of Polyarteritis nodosa. Clinical course and management with steroid and cytotoxic therapy. Ophthalmology 1993; 100: 1775.
24. Hsu CT, Kerrison JB, Miller NR, Goldberg MF. Choroidal infarction, anterior ischemic optic neuropathy, and central retinal artery occlusion from Polyarteritis nodosa. Retina 2001; 21: 348.
25. Leavitt RY, Fauci AS. Polyangitis overlap syndrome. Classification and prospective clinical experience. Am J Med 1986; 81: 79.

© 2016 Global Journals Inc. (US)

This page is intentionally left blank

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

By Okeh UM & Oyeka ICA
Nnamdi Azikiwe University Awka

Abstract- This paper proposes and presents a method for the estimation of approval probabilities of new drug or product. The proposed method assumes that three evaluation communities are used to assess and evaluate the quality of a new drug or product and that the evaluation is done by the committees in three period phased clinical trials of the drug product using matched samples of subjects at each phase. Estimates of absolute and conditional approval probabilities by various combination evaluation committees at each phase of clinical trials are provided. Test statistics are also developed testing desired hypothesis at each of the phased clinical trials.

The proposed method is illustrated with some sample data. It is shown in terms of estimated probability that it is more difficult for all three evaluation committees to be in complex agreement to approve or not approve a new drug or product than for fewer evaluation committees to grant approval.

Keywords: evaluation committees, product, volunteer, probabilities, phased controlled clinical trials, diagnostic screening tests.

GJMR-F Classification: NLMC Code: QV745

Strictly as per the compliance and regulations of:

© 2016. Okeh UM & Oyeka ICA. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/ 3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

Okeh UM [α] & Oyeka ICA [σ]

Abstract- This paper proposes and presents a method for the estimation of approval probabilities of new drug or product. The proposed method assumes that three evaluation communities are used to assess and evaluate the quality of a new drug or product and that the evaluation is done by the committees in three period phased clinical trials of the drug product using matched samples of subjects at each phase. Estimates of absolute and conditional approval probabilities by various combination evaluation committees at each phase of clinical trials are provided. Test statistics are also developed testing desired hypothesis at each of the phased clinical trials.

The proposed method is illustrated with some sample data. It is shown in terms of estimated probability that it is more difficult for all three evaluation committees to be in complex agreement to approve or not approve a new drug or product than for fewer evaluation committees to grant approval.

Keywords: evaluation committees, product, volunteer, probabilities, phased controlled clinical trials, diagnostic screening tests.

I. Introduction

As observed in Onyiora et al (2013) most health care professionals would want their patients to have the best available clinical care but the problem these professional often have is the inability to clearly identify the optimum drug or intervention procedure to adopt in patient treatment and management and often rely on own experience or these of colleagues in actual practice. However, health professionals are increasingly relying on evidence based medical and health practices hinged on a systematic revision evaluation, evaluation, assessment and application of clinical research findings (Rising, Bacchetti and Baro,2009;Chow and Liu,2004).

In medical practice and health management, erroneous and misguided approval of a new drug or product is often hazardous and costly in human and material resources (Gobburn and Leske, 2009).

Following a sequence of clinical trials often conducted in phases by evaluation bodies or committees, approval of a new drug or product for use in a population may be granted if the drug or product satisfies some set of predetermined criteria for use (Haff, 2003). In controlled clinical trials of new drug or product using cross sectional, prospective or retrospective study methods, the trials are usually conducted in phases using usually test animals and subsequently volunteer human subjects (Onyiora et al, 2013; Lipkovic et al, 2008). Approval for use of a new drug product in a population is granted only after the phased clinical trials the proportion of subjects improving with the new drug or product is higher than the proportion improving with the standard drug under all or most of the evaluation committees involved in the phased clinical trials.

Following the phased clinical trial procedures, specifically using the three period phased clinical trials by three evaluation committees. Onyiora et al (2013) proposed and developed a probability model that would enable the calculation of the proportion or probabilities of approving or not approving new drug or product by none, some or all the evaluation committees.

The probability estimation model developed the authors is however most useful if the probabilities a-g are given or already be used in the estimation of the probabilities of possible outcomes including the outcomes or evenly listed in the authors' Table 2.The method under reference does not however provide a method to use in the a-priori estimate of the probabilities 'a-g' if not already given and are not known, and must be estimated from sample data obtained in relevant count phased clinical test trials of a new drug or product.

In this paper we propose to develop a more generalized method for the estimation of probabilities of outcomes in phased controlled clinical trials of a drug or product by three evaluation committees. The present method would readily enable one estimate probabilities of approval or non-approval of a new drug or product using sample data obtained in three phased clinical trials by three evaluation committees: cross-section, prospective or retrospective clinical trials conducted in three phases. Now to conduct the clinical trials, matched random samples of consenting subjects or volunteers matched by age, sex, body weight and other demographic characteristics are to be used. If the study is a retrospective one then the required data would of course be obtained from case history files of the study participants. Suppose in the first phase of the controlled clinical trials each of the evaluation committees tests, screens or administers a new drug or product to a different but comparable sample of such matched

Author α: Department of Industrial Mathematics and Applied Statistics, Ebonyi State University Abakaliki Nigeria.
e-mail: uzomaokey@ymail.com
Author σ: Department of Statistics, Nnamdi Azikiwe University Awka, Nigeria.

© 2016 Global Journals Inc. (US)

samples of subjects of equal sizes n_1.In the second phased of the clinical trials three samples of the three cooperating approval agencies, three equal samples of size n_2.

II. Proposed Method

To develop a method for use in estimating probabilities that may help in the assessment and evaluation of a new drug or product for possible approval for use in a population when these probabilities are not a-preen given, we may assume following Onyiorah et al (2013) (that three mutually co-operating evaluation bodies or committees x, y and z co-operating in the sense that they employ the same evaluation criteria used for the drug or product quality assessment or evaluation) phased controlled clinical trials. The evaluation would be done using controlled cross-sectional comparative either prospective or retrospective study in clinical trials conducted in three phases. Now to conduct the clinical trails, matched random samples of consenting subjects or volunteers matched by age, sex, body weight and other demographic characteristics are to be used. If the study is a retrospective one then the required data would of course be obtained from case history files of the study participants. Suppose in the first phase of the controlled clinical trials each of the evaluation committees tests, screens or administers a new drug or product to a different but comparable sample of such matched samples of subjects of equal sizes,n_1.In the second phase of the clinical trials samples of three equal samples of size n_2 matched pairs of subjects matched on the same demographic characteristics as in the first phase of the trials are used pairs of the three co-operating evaluation committees are assigned to test, screen or treat members in one of each of the three paired samples of matched subjects, with one evaluation committee in each pair testing the first members say of each paired sample of subjects and the other member of the paired evaluation committees testing the second members, say of the paired sample of subjects assigned to that evaluating committee.

In the third and last phase of the clinical trials matched triples of size n_3 subjects are used. That is n_3 samples each of three matched subjects are used. One subject in each matched triple, that is one subject in each of three matched subjects is tested, screened or treated by one of the three evaluation committees.

Now as in Onyiorah et al (2013), suppose A and $\bar{A}$ are respectively the events that evaluation committee X approves and does not approve a new drug or product for use; $B \text{ and } \bar{B}$ are respectively the events that evaluation committee Y approves and does not approve a new drug or product for use; and $C \text{ and } \bar{C}$ are respectively the events that evaluation committee Z approves and does not approve a new drug or product for use in a population. To develop a method for the estimation of new drug or product approval probability assuming that three mutually cooperating evaluation committees X,Y and Z are used in clinical trials conducted in three phases to assess the quality of the drug or product for possible approval, we may proceed as follows:

For the first phase of the clinical trials, considering drug assessment by evaluation committees X say we may let

$$u_{ix} = \begin{cases} 1, \ if \ the \ ith \ subject \ tested, screened \ or \ ad\min istered \\ a \ new \ drug \ by \ evaluation \ committee \ X \ responds \ positive \\ 0, otherwise \end{cases} \quad (1)$$

$$for \ i = 1, 2, \ldots n_i$$

Let

$$\pi_x^+ = P(u_{ix} = 1) \quad (2)$$

Also define

$$W_x = \sum_{i=1}^{n_1} u_{ix} \quad (3)$$

Now the expected value and variance of u_{ix} are respectively

$$E(u_{ix}) = \pi_x^+; Var(u_{ix}) = \pi_x^+(1-\pi_x^+) \quad (4)$$

Also the expected value and variance of W_x are respectively.

$$E\ W_x = \sum_{i=1}^{n_1} E\ u_{ix} = n_1\ \pi_x^+ \quad Var\ W_x = \sum_{i=1}^{n_1} Var\ u_{ix} = n_1\ \pi_x^+ - \pi_x^+ \quad (5)$$

© 2016 Global Journals Inc. (US)

Now π_x^+ is the proportion on probability that on the average subjects tested, screened or treated by evaluation committee X responds positive. Its sample estimate is

$$\hat{\pi}_x^+ = P_x = \frac{W_x}{n_1} = \frac{f_x^+}{n_1} \quad 6$$

where f_x^+ is the number of subjects responding positive under evaluation committee X, that is when tested by evaluation committee X. This f_x^+ is the total number of 1s in the frequency distribution of the n_1 values of 0s and 1s in u_{ix} for i=1,2,…n_1.

The sample estimate of the variance of $\hat{\pi}_x^+$ is from Equation 5

$$Var(\hat{\pi}_x^+) = Var\frac{(W_x)}{n_1^2} = \frac{\hat{\pi}_x^+(1-\hat{\pi}_x^+)}{n_1} \quad 7$$

A null hypothesis that may often be of interest could be that the proportion π_x^+ of subjects responding positive under evaluation committee X is at most some value π_{xo}, or symbolically:

$$H_0 : \pi_x^+ \leq \pi_{xo} \ versus \ H_1 : \pi_x^+ > \pi_{xo} (0 \leq \pi_{xo} \leq 1) \quad 8$$

The null hypothesis H_0 of Equation 8 may be tested using the test statistic

$$\chi^2 = \frac{(W_x - n_1.\pi_{xo})^2}{Var(W_x)} = \frac{n_1(\hat{\pi}_x^+ - \pi_{xo})^2}{\hat{\pi}_x^+(1-\hat{\pi}_x^+)} \quad 9$$

Which under H_0 has approximately the chi-square distribution with 1 degree of freedom for sufficiently large n_1.The null hypothesis H_0 of equation 8 is rejected at α level of significance if

$$\chi^2 \geq \chi^2_{1-\alpha;1} \quad 10$$

Otherwise H_0 is accepted. To estimate the probability of approval of a new drug or product by evaluation committee Y during the first phase of clinical trials we may let

$$u_{iy} = \begin{cases} 1, if \ the \ subject \ tested, screened \ or \ treated \ with \ a \ new \ drug \ or \ product \\ by \ evaluation \ committee \ approved \ agency \ Y \ responds \ positive \\ 0, otherwise \end{cases} \quad 11$$

$$for \ i = 1, 2, ..., n.$$

Let

$$\pi_y^+ = P(u_{iy} = 1) \quad 12$$

And

$$W_y = \sum_{i=1}^{n_1} u_{iy} \quad 13$$

Now

$$E(u_{iy}) = \pi_y^+; Var(u_{iy}) = \pi_y^+(1-\pi_y^+) \quad 14$$

And

$$E(W_y) = n_1.\pi_y^+; Va\ (W_y) = n_1.\pi_y^+(1-\pi_y^+) \quad 15$$

For evaluation committee Y approved agency, π_y^+ is the proportion of subjects responding when tested, screened or administered by evaluation committee Y during the first phase of clinical trials.
Its sample estimate is

© 2016 Global Journals Inc. (US)

$$\hat{\pi}_y^+ = p_y = \frac{W_y}{n_1} = \frac{f_y^+}{n_1} \quad (16)$$

where f_y^+ is the number of subjects responding positive to evaluation committee Y in the first phase of clinical trials which is the total number of 1s in u_{iy} , $i = 1, 2, .., n_1$.

The corresponding sample variance is

$$Var\ (\hat{\pi}_y^+) = \frac{Var(W_y)}{n_1^2} = \frac{\hat{\pi}_y^+(1-\hat{\pi}_y^+)}{n_1} \quad (17)$$

A null hypothesis similar to that of Equation 17 for evaluation committee X may also be stated and tested for evaluation committee approval agency.

Following similar approaches as above, we also develop sample estimate approval probability π_z^+ for evaluation committee agency Z as

$$\hat{\pi}_z^+ = p_z = \frac{W_z}{n_1} = \frac{f_z^+}{n_1} \quad (18)$$

Where f_z^+ is the number of subjects responding positive when tested, screened or administered a new drug or products evaluation committee approval agency Z during the first phase of clinical trials. The corresponding sample variance is similarly estimated.

Note that $\pi_x^+, \pi_y^+ and\ \pi_z^+$ are respectively the equivalence of 0,1 in Onyiorah et al(2013).

To estimate conditional probabilities of approval of a new drug or product by the evaluation committees X,Y and in the second phase of clinical trials, we may first suppose that of the n_2 matched paired samples of subjects used in this phase of trials $n_{y.x}\ and\ n_{z.x}$ subjects respond positive to the drug or product when tested by evaluation committee Y and Z respectively; and $n_{z.y}$ subjects respond positive under evaluation committees Y when paired with evaluation committee Z.

To estimate conditional probabilities of approval of a new drug or product by any pair of evaluation committees X and Y say during the second phase of clinical trials, we may let

$$u_{iy.x} = \begin{cases} 1, if\ for\ the\ ith\ pair\ of\ subjects\ tested\ by\ evaluation\ committees \\ X\ and\ Y\ during\ the\ second\ phase\ of\ trials, the\ subjects\ tested\ by\ evaluation \\ committee\ Y\ responds\ positive\ given\ that\ the\ corresponding\ subject \\ in\ the\ pair\ tested\ by\ evaluation\ committee\ X\ has\ also\ responded\ positive \\ 0, otherwise \end{cases} \quad (19)$$

$$for\ i = 1, 2, ..., n_x$$

Let

$$\pi_{yx}^+ = P(u_{iy.x} = 1) \quad (20)$$

$$And$$

$$W_{y.x} = \sum_{i=1}^{n_{y.x}} u_{iy.x} \quad (21)$$

The expected value and variance of $u_{iy.x}$ are respectively

$$E(u_{iy.x}) = \pi_{y.x}^+; Var(u_{iy.x}) = \pi_{y.x}^+(1-\pi_{y.x}^+) \quad (22)$$

Also the expected value and variance of $W_{y.x}$ are respectively

$$E(W_{y.x}) = \sum_{i=1}^{n_{y.x}} E(u_{iy.x}) = n_{y.x}\pi_{yx}^+; Var(W_{y.x}) = \sum_{i=1}^{n_{yx}} Var(u_{iy.x}) = n_{y.x}\pi_{yx}^+(1-\pi_{yx}^+) \quad (23)$$

Now π_{yx}^+ is the proportion or probability that on the average in the pairs of subjects tested by evaluation committees X and Y during the second phase of clinical trials subjects tested by evaluation committee Y respond

© 2016 Global Journals Inc. (US)

positive given that the corresponding subjects tested by evaluation committee X have also responded positive to the new drug product. Its sample estimate is

$$\pi_{yx}^{+} = P_{yx} = \frac{W_{y.x}}{n_{y.x}} = \frac{f_{y.x}^{+}}{n_{y.x}} \quad 24$$

Where $f_{y.x}^{+}$ is the number of pairs of subjects for which subjects tested in the pairs by evaluation committee Y respond positive given that the corresponding subjects in the same pairs treated by evaluation committee X have also responded positive to the drug or product in the second phase of clinical trials. Thus $f_{y.x}^{+}$ is the total number of 1s in the frequency distribution of the n_{yx} values of 0s and 1s in $u_{iy.x}$ for $i = 1,2,\ldots,n_x.$

The sample variance of $\hat{\pi}_{y.x}^{+}$ is from Equation 23

$$Var\left(\hat{\pi}_{y.x}^{+}\right) = \frac{Var\left(W_{y.x}\right)}{ny_{y.x}^{2}} = \frac{\hat{\pi}_{y.x}^{+}\left(1-\hat{\pi}_{y.x}^{+}\right)}{n_x} \quad 25$$

For the second phase of clinical trials, the null hypothesis that may be of interest concerning evaluation committees approved agencies X and Y say may be that the proportion of subjects responding positive when tested by evaluation committee Y given positive response under evaluation committee agency X is at least some value $\pi_{y.x_0}^{+}$, that is the null hypothesis

$$H_0 : \pi_{y.x}^{+} \geq \pi_{y.x_0}^{+} \; versus \; H_1 : \pi_{y.x}^{+} < \pi_{y.x_0}^{+}, (0 \leq \pi_{y.x_0}^{+} \leq) \quad 26$$

The null hypothesis H_0 of Equation 26 may be tested using the test statistic

$$\chi^2 = \frac{\left(W_{y.x} - n_x \pi_{yx_0}\right)^2}{Var\left(W_{y.x}\right)} = \frac{n_x(\hat{\pi}_{y.x}^{+} - \pi_{yx_0})^2}{\hat{\pi}_{y.x}^{+}(1-\hat{\pi}_{y.x}^{+})} \quad 27$$

Which has approximately the chi-square distribution with 1 degree of freedom for sufficiently large n_{yx} .The null hypothesis H_0 is rejected at the α level of significance if Equation 10 is satisfied otherwise H_0 is accepted.

To estimate conditional probability of positive response under evaluation committees X and Z we may let

$$u_{iz.x} = \begin{cases} 1, if \;\; for \; the \; ith \;\; pair \; of \;\; subjects \; tested \; by \; evaluation \\ committtees \;\; X \;\; and \;\; Z \; in \; the \; \text{second} \;\; phase \; of \;\; trials, \\ the \; subject \; tested \; by \; evaluation \; commmittees \; Z \; responds \\ positive \; given \; that \; the \; corresponding \; subject \; tested \; by \; evaluation \\ committee \;\; X \;\; has \; also \; responded \;\; positive \\ 0, otherwise \end{cases} \quad 28$$

$$for \; i = 1,2,....,n_x$$

Let

$$\pi_{z.x}^{+} = p(u_{iz.x} = 1) \quad 29$$

$$And$$

$$W_{Z.x} = \sum_{i=1}^{n_{z.x}} u_{iz.x} \quad 30$$

$$Now$$

$$E(u_{iz.x}) = \pi_{z.x}^{+}; Var(u_{iz.x}) = \pi_{z.x}^{+}(1-\pi_{z.x}^{+}) \quad 31$$

$$And$$

$$E\left(W_{Z.x}\right) = n_{zx}.\pi_{z.x}^{+}; Var(W_{Z.x}) = n_{zx}.\pi_{z.x}^{+}(1-\pi_{z.x}^{+}) \quad 32$$

© 2016 Global Journals Inc. (US)

Note that $\pi^{+}_{z.x}$ is the proportion on conditional probability that in the paired samples of subjects tested by evaluation committees X and Z respectively also respond positive to the new drug or product during the third phased of clinical trials. Its sample estimate is

$$\pi^{+}_{y.xz} = P_{y.xz} = \frac{W_{y.xz}}{n_{y.xz}} = \frac{f^{+}_{y.xz}}{n_{y.xz}} \quad 33$$

Where $f^{+}_{y.xz} = W_{y.xz}$ is the number of matched triples of subjects in which the subjects tested in phase three by evaluation committee Y respond positive given that the other two subjects in the matched triples tested by evaluation committee X and Z respectively have also responded positive, which is also really the total number of 1s in $u_{iy.xz}, i = 1, 2, ..., n_{y.xz}$.

The sample estimate of the variance of $\hat{\pi}^{+}_{y.xz}$ is

$$Var(\hat{\pi}^{+}_{y.xz}) = \frac{Var(W_{y.xz})}{n^{2}_{y.xz}} = \frac{\pi^{+}_{y.xz}(1-\pi^{+}_{y.xz})}{n_{y.xz}} \quad 34$$

Again if of research interest a null hypothesis similar to that of Equation 26 may be stated and similarly tested for $\pi^{+}_{y.xz}$. Similar procedures as above would also enable us obtain sample estimate of the conditional probability that during the third phase of clinical trials by evaluation committees X,Y and Z for subjects in the matched triples of subjects tested by these committees the subjects tested by evaluation committee X respond positive given that corresponding subjects in the matched triples tested by evaluation committees Y and Z respectively also respond positive. This conditional probability is estimated as

$$\hat{\pi}^{+}_{x.yz} = P_{x.yz} = \frac{W_{x.yz}}{N_{x.yz}} = \frac{f^{+}_{x.yz}}{n_{x.yz}} \quad 35$$

Where $f^{+}_{x.yz} = W_{x.yz}$ is the number of matched triples of subjects, that is matched samples of three subjects in which subjects tested in phase three by evaluation committee X respond positive given that the other two subjects in the matched triples tested by evaluation committees Y and Z respectively also test positive to the new drug or product in the third phase of controlled clinical trials.

The sample estimate of the variance of $\hat{\pi}^{+}_{x.yz}$ is similarly obtained as

$$Var(\hat{\pi}^{+}_{x.yz}) = \frac{Var(W_{x.yz})}{n^{2}_{x.yz}} = \frac{\hat{\pi}^{+}_{x.yz}(1-\hat{\pi}^{+}_{x.yz})}{n_{x.yz}} \quad 36$$

Again if of research interest a null hypothesis similar to that of Equation 26 may also be stated and similarly tested for $\pi^{+}_{x.yz}$.

Note again that by the specifications adopted above, the present sample estimates of the conditional probabilities $P(C/AB), P(B/AC)$ *and* $P(A/BC)$ namely $\pi^{+}_{z.xy}, \hat{\pi}^{+}_{y.xz}$ *and* $\hat{\pi}^{+}_{x.yz}$ as respectively

$$\hat{\pi}^{+}_{z.xy} = P_{z.xy}; = \hat{\pi}^{+}_{y.xz} = P_{y.xz} \text{ and } \hat{\pi}^{+}_{x.yz} = P_{x.yz} \quad 37$$

Other conditional probabilities may be similarly estimated as desired.

If stringencies in terms of high approval probability is a desired and preferred criterion for new drug or product use approval, then in the third phase of clinical trials the outcome or event C/AB, say is more desirable and preferable to event B/AC, say if and only if P(C/A)>P(B/A).This is because if event C/AB is more preferable to event B/AC, then

$$P(C/AB) = \frac{P(ABC)}{P(AB)} > \frac{P(ABC)}{P(AC)} = P(B/AC).$$

So that

$$\frac{1}{P(AB)} = \frac{1}{P(A).P(B/A)} > \frac{1}{P(A).P(C/A)} = \frac{1}{P(AC)}$$

Hence

$$P(C/A) > P(B/A).$$

On the other hand if $P(C/A) > P(B/A)$, then clearly $P(C/AB) > P(B/AC)$.

© 2016 Global Journals Inc. (US)

Stated in terms of sample estimates of probabilities, this would mean that in the third phase of three phased controlled clinical trials of a new drug or product by these evaluation committee X,Y and Z.

V if and only if in the second phase of clinical trials $P_{z.x} > P_{y.x}$

Other conditional probabilities may be similarly estimated as desired.

Now we have so far presented the probability estimation procedures generally under the assumption that all three evaluation committees are equally competent in experience or otherwise to assess and evaluate new drug or product. In really however some evaluation committees may be better qualified, experienced, with higher expertise, better equipped etc, than others and hence may play supervisory roles and be able to obtain more reliable results.

Hence we may but without loss of generality assume that three evaluation committees used here can be ordered in terms of experience and seniority in assessment, evaluation and approval of now drugs or products ranked from the most senior down to the least senior. Thus we may again but without loss of generality assume that evaluation committee X is the most senior followed by evaluation committees Y and Z in this order. This would in effect mean that any drug or product approved by evaluation committee Z would be subject to further approvals by evaluation committee Y and finally by evaluation committee X.

Under these assumptions the probabilities already estimated above would be sufficient to estimate the required overall approval probability after the third and last phase of controlled clinical trials.

Never the-less the present probability estimation model would enable the estimation of the probabilities of all events that can possibly be obtained in the event space of all conceivable outcomes in phased controlled clinical trials. For example the probability that say evaluation committees X and Y do not approve a new drug or product given that evaluation committee Z approves, is the probability of the event $(\bar{A}\bar{B}/C)$ which is

$$P(\bar{A}\bar{B}/C) = P(C) - P(A).P(C/A) - P(B).P(C/B) + P(C/AB).P(B/A).P(A)P(C)$$

OR

In terms of estimated probabilities,

$$P(\bar{A}\bar{B}/C) = P_z - P_x.P_{z.x} - P_yP_{z.y} + P_{z.xy}.P_{y.x}.P_x \ etc.$$

However in this section, if interest is only in the estimation of the probabilities of the events, then these are obtained using the marginal and conditional probabilities already estimated above, namely

$$P(A) = a = P_x; P(B) = b = P_y; P(C) = c = P_c \quad 38$$

And

$$P(B/A) = d = P_{y.x}; P(C/A) = e = P_{z.x}; P(C/B) = f = P_{z.y}; P(C/AB) = g = P_{z.xy} \quad 39$$

With these results the probability that all the three evaluation committees X,Y and Z approved a new drug or product is the probability of the event $S_3 = (ABC)$ which is estimated using sample values obtained above as

$$P(ABC) = P(C/AB).P(B/A).P(A) = P_{z.xy}; P_{y.x}; P_x \quad 40$$

If at least two evaluation committees must approve a new drug or product before use, then the corresponding events set is $S_2 = (ABC, AB\bar{C}, \bar{A}BC)$ whose probability is easily shown to be

$$P(S_2) = P_x.P_{y.x} + P_x.P_{z.x} + P_y.P_{z.y} - 2P_{z.xy}.P_{y.x}P_x \quad 41$$

If there is a supervising evaluation committee such as evaluation committee X who must approve in addition to at least one other evaluation committee before a new drug or product is considered approved for use, then the required events set is $S_x = (ABC, AB\bar{C}, A\bar{B}C)$ whose sample estimate is

$$P(S_x) = P_x.P_{yx} + P_xP_{z.x} - P_{z.xy}P_{yx}..P_{x.} \quad 42$$

The probability that evaluation committees Y and Z approve a drug or product evaluation committee X does not approve it is the probability of the event, $S_{yz} = (\bar{A}BC)$ which is estimated as

$$P(S_{yz}) = P(\bar{A}.B.C) = (1 - P(A/BC)).P(BC) = P(C/B).P(B) - P(ABC),$$

which when expressed in terms of sample probabilities becomes

© 2016 Global Journals Inc. (US)

$$P(S_{yz}) = P_y.P_{zy} - P_{z.xy}P_{y.x}.P_x$$ 43

The probability that none of the evaluation committees approves a drug or product for use is the probability of the event $S_0 = (\bar{A}\bar{B}\bar{C})$ which is

$$P(S_0) = P(\bar{A}\bar{B}\bar{C}) = 1 - \left(P(A) + P(B) + P(C) - P(B/A).P(A) - P(C/A).P(A) - P(C/B).P(B) + P(ABC)\right)$$

Which when evaluated in terms of sampled estimates becomes

$$\boldsymbol{P(S_0) = 1 - \left(P_x + P_y + P_z - P_xP_{yx} - P_xP_{zx} - P_yP_{z.y} + P_{z.xy}P_{y.x}P_x\right)}$$

Other probabilities are similarly estimated the results are shown in Table 1

Table 1: Sample Estimates of New Drug or Product Approval Probabilities by three evaluation Committees in Phased Clinical Trials

S/No	Event	Approval Probability
1	ABC	$P_{z.xy}.P_{y.x}P_x$
2	$AB\bar{C}$	$P_xP_{y.x} - P_{z.xy}P_{y.x}.P_x$
3	$A\bar{B}C$	$P_xP_{z.x} - P_{z.xy}P_{y.x}.P_x$
4	$A\bar{B}\bar{C}$	$P_x - P_x.P_{z.x} - P_xP_{y.x} + P_{z.xy}P_{y.x}.P_x$
5	$\bar{A}BC$	$P_y.P_{z.y} - P_{z.xy}.P_{yx}P_x$
6	$\bar{A}B\bar{C}$	$P_y - P_y.P_{z.y} - P_x.P_{y.x} + P_{z.xy}.P_{y.x}.P_x$
7	$\bar{A}\bar{B}C$	$P_z - P_x.P_{z.y} - P_y.P_{z.y} + P_{z.xy}.P_{y.x}.P_{y.x}$
8	$\bar{A}\bar{B}\bar{C}$	$1 - \left(P_x + P_y + P_x.P_{yx} - P_x.P_{zx} - P_yP_{z.y} + P_{z.xy}.P_{y.x}.P_x\right)$
9	S_2(at least two Evaluation; committees)	$P_xP_{y.x} + P_x.P_{z.x} + P_y.P_{z.y} - 2P_{z.xy}.P_{y.x}.P_{y.x}$
10	S_x(Evaluation Committee X;and at least on another)	$P_xP_{y.x} + P_x.P_{z.x} - P_{z.xy}.P_{y.x}.P_x$
11	Sy(Evaluation Committee Y and at least one other)	$P_xP_{y.x} + P_y.P_{z.y} - P_{z.xy}.P_{y.x}.P_x$
12	Sz(Evaluation Committee Z and at least one other)	$P_yP_{z.y} + P_x.P_{z.x} - P_{z.xy}.P_{y.x}.P_x$

Teams of research scientists in the Department of Pharmacology of three Universities X,Y and Z were interested in conducting phased controlled prospective clinical trials on a certain herb product believed by a local population to be effective in the treatment of malaria. In the first phase of clinical trials the three research teams collected three random samples each of size 40 of volunteer malaria patients matched on age, gender and body mass index(BMI),and each research team or committee team administered appropriately determined dosages of the herb product each on patients in only one of the three matched samples.

In the second phase of clinical trials three matched pairs of patients each of size 30 were used. The three research teams were also then paired. Each pair of the research team administered dosages of the herb product to one paired sample of patients with one research team administering the dosage to say the first patient in each pair and the other research team administering the dosage to the remaining patient in the pair.

In the third phase of clinical trials 25 samples of matched triples of patients, that is 25 samples each of three matched patients were used. The three research teams each administered dosages of the herb product to only one patient in each of the 25 matched triples of patients. At the end of each phase of the clinical trials the research scientists assesses the malaria patients as either recovered (R) or not recovered (N) obtaining the results shown in Table 2.

© 2016 Global Journals Inc. (US)

Table 2: Patient Response in Phase One clinical trials of Anti-Malaria Herb Product by Three Research Teams

S/No	Team 1(Sample 1)	Team 2(Sample 2)	Team 3(Sample 3)
	X	Y	Z
1	R	N	R
2	R	R	N
3	R	N	N
4	N	R	R
5	R	R	R
6	R	N	R
7	N	R	N
8	N	N	N
9	N	N	R
10	N	R	R
11	N	N	N
12	R	N	R
13	N	R	R
14	R	R	R
15	N	N	R
16	R	N	N
17	R	R	N
18	R	R	R
19	N	R	R
20	R	N	R
21	N	N	N
22	R	R	R
23	N	R	N
24	R	R	R
25	N	R	N
26	R	N	R
27	R	R	R
28	R	R	N
29	R	R	N
30	R	R	N
31	N	R	R
32	R	N	R
33	N	R	N
34	R	R	N
35	N	R	R
36	N	N	N
37	N	N	R
38	R	N	N
39	R	N	R
40	R	N	N
n_i	40	40	40
f_l^+	$23(f_x^+)$	$22(f_y^+)$	$22(f_z^+)$
$\hat{\pi}_l^+$	$0.575(\hat{\pi}_x^+)$	$0.550(\hat{\pi}_y^+)$	$0.550(\hat{\pi}_z^+)$

Table 3: Patient Response in Phase Two Clinical Trials of Malaria Herb Product by Three Research Teams

	Matched Pair Team 1		Matched Pair Team 2		Matched Pair Team 3	
	X	Y	X	Z	Y	Z
1	N	N	R	N	N	N
2	R	R	N	R	R	R
3	R	R	R	R	N	R
4	N	R	R	N	R	R
5	N	R	N	R	R	R
6	R	N	R	R	N	R

© 2016 Global Journals Inc. (US)

7	N	R	N	R	R	N
8	N	N	N	N	R	R
9	R	N	R	R	R	R
10	N	N	R	N	N	N
11	N	N	R	R	N	R
12	R	N	N	R	N	N
13	R	N	N	N	R	N
14	R	R	R	R	N	N
15	N	R	N	R	N	N
16	N	N	R	N	R	R
17	R	N	R	R	R	R
18	N	N	R	R	R	N
19	N	R	N	N	N	N
20	N	N	N	N	N	N
21	N	R	R	N	N	N
22	R	N	R	N	N	R
23	N	N	R	R	R	N
24	R	R	R	N	R	R
25	N	R	N	N	N	R
26	N	R	N	R	N	R
27	N	R	N	N	R	N
28	R	N	R	N	R	R
29	N	N	R	R	R	R
30	R	N	R	R	R	R
$n_{k.j}$	$12(n_{y.x})$		$18(n_{z.x})$		$16(n_{z.y})$	
$f^{+}_{k.j}$	$4(f^{+}_{y.x})$		$10(f^{+}_{z.x})$		$11(f^{+}_{z.y})$	
$\hat{\pi}^{+}_{k.j}$	$0.333(\hat{\pi}^{+}_{y.x})$		$0.556(\hat{\pi}^{+}_{z.x})$		$0.688(\hat{\pi}^{+}_{z.y})$	

Table 4: Patient Response in Phase Three Clinical Trials of Anti-Malaria Herb Product by Three Research Teams

Matched Triple	Research Team X	Research Team Y	Research Team Z
1	N	R	N
2	R	N	N
3	R	R	N
4	N	R	R
5	N	N	R
6	R	R	R
7	N	N	N
8	N	R	N
9	R	R	R
10	N	N	N
11	N	N	N
12	N	N	R
13	R	R	N
14	R	N	N
15	N	N	N
16	R	R	R
17	N	N	R
18	R	N	R
19	R	N	N
20	N	N	R
21	N	R	N
22	N	R	N
23	R	R	R
24	N	R	R
25	N	R	R
$n_{k.lj}$	$8(n_{x.yz})$	$5(n_{y.xz})$	$6(n_{z.xy})$

© 2016 Global Journals Inc. (US)

$f^+_{k.lj}$	$4(f^+_{x.yz})$	$4(f^+_{y.xz})$	$4(f^+_{z.xy})$
$\hat{\pi}^+_{k.lj}$	$0.500(\hat{\pi}^+_{x.yz})$	$0.800(\hat{\pi}^+_{y.xz})$	$0.667(\hat{\pi}^+_{z.xy})$

We here use the sample data of Table 2-4 to illustrate the present probability estimation method.

Thus applying the methods to the data we have as shown at the bottom of Table 2 with $n=n_1=40$,that

$$f^+_x = 23;\ f^+_y = 22\ and\ \ f^+_z = 22; so\ that\ \hat{\pi}^+_x = P_x = 0.575(= a);$$

$$\hat{\pi}^+_y = P_y = 0.550(= b); and \hat{\pi}^+_z = P_z = 0.550(= c).$$

From Table 3 we have that

$$n_{y.x} = 12; n_{z.x} = 18, and\ n_{z.y} = 16$$

Also

$$f^+_{y.x} = 4;\ f^+_{z.x} = 10;\ f^+_{z.y} = 11.$$

Hence

$$\hat{\pi}^+_{y.x} = P_{y.x} = 0.333(= d); \hat{\pi}^+_{z.x} = P_{z.x} = 0.556(= e); and\ \hat{\pi}^+_{z.y} = P_{z.y} = 0.688(= f).$$

Finally from Table 4 we have that

$$n_{z.xy} = 6\ and\ \ f^+_{z.xy} = 4$$

Hence

$$\hat{\pi}^+_{z.xy} = P_{z.xy} = 0.667(= g).$$

Note also from Table 4 that

$$n_{y.xz} = 5, n_{x.yz} = 8;\ f^+_{y.xz} = f^+_{x.yz} = 4\ so\ that\ \hat{\pi}^+_{y.xz} = P_{y.xz} = 0.800;\ and\ \hat{\pi}^+_{x.yz} = P_{x.yz} = 0.500.$$

These probability estimates are now used with Table 1 to obtain sample estimates of some possible outcomes in three phased controlled clinical trials of a product, namely anti-malaria herb product.

The estimates are presented in Table 5.

Table 5: Sample Estimates of Probabilities of the events of Table 1 for anti-malaria herb product

S/No	Event	Estimated Approval Probability
1	ABC	0.127
2	$AB\bar{C}$	0.064
3	$A\bar{B}C$	0.193
4	$A\bar{B}\bar{C}$	0.191
5	$\bar{A}BC$	0.251
6	$\bar{A}B\bar{C}$	0.108
7	$\bar{A}\bar{B}C$	0.021
8	$\bar{A}\bar{B}\bar{C}$	0.079
9	S_2(at least two evaluation committee)	0.635
10	S_X(evaluation committee and at least one other)	0.384
11	S_Y(evaluation committee and at least one other)	0.442
12	S_Z(evaluation committee and at least one other)	0.571

It is seen from Table 2 that in the first phase of controlled clinical trials, evaluation committee X approved the anti-malaria herb product with an estimated probability of 0.575 while evaluation

© 2016 Global Journals Inc. (US)

committees Y and Z approved the drug with equal probability of 0.550.

In the second phase of clinical trials (Table 3 given that evaluation committee X has approved the drug, evaluation committees Y and Z are found to approve the drug with estimated probabilities of 0.333 and 0.556 respectively while if evaluation committee Y has already approved the drug, then evaluation committee Z would be expected to approve the drug with probability 0.688.

In the third phase of clinical trials (Table 4) it is seen that if evaluation committees X and Y have already approved the drug, then evaluation committee Z would approve the drug with an estimated probability of 0.667 while evaluation committee Y would approve with estimated probability of 0.800 if evaluation committees X and Z have already granted the approval.

From Table 5, it is seen that if all three evaluation committees are required to grant approval before a new drug or product (anti-malaria herb product)can be approved for use in a population then the estimated probability of such an approval being granted is only 12.7 percent, which is relatively more stringent compared with when only two evaluation committees are required to grant approval with an estimated probability of

$$(.0575)(0.333)+(0.575)(0.556)+(0.530(0.688)-3(0.127)=0.889=0.381=0.508,$$

which is relatively more liberal.

Note from Table 5 that at the end of the third phase of clinical trials if the drug must be approved by at least one evaluation committee as the supervisory committee, then evaluation committee X is seen to be the most stringent with an estimated overall probability of approval of only 38.4 percent while evaluation committee Z is the most liberal with an estimated overall probability of approval of as high as 57.1 percent.

It is found that just as the probability of three evaluation committees completely agreeing approve drug after the third phase of clinical trials is rather small at 0.127, the probability of three committees being in complete agreement not to approve the drug is even much smaller with an estimated value of only 7.9 percent.

III. Summary and Conclusion

We have in this paper developed and presented statistical method that would enable the estimation of probabilities of approving and not approving a new drug or product for possible use in a population under the assumption that three evaluation committees are used to assess and evaluate the drug or product in clinical trials conducted in three phases. At each phase of clinical trials evaluation committees used matched samples of subjects for drug or product quality evaluation or assessment.

Test statistics were developed for testing any desired hypothesis about approval probabilities each phase of clinical trials. The proposed method was illustrated with some sample data and the results show that the probabilities of three evaluation committees being in complete agreement to approve and not approve a new drug or product are likely to be much smaller than the probabilities that only some of the three evaluation committees approve the drug or product

References Références Referencias

1. Rising K, Bacchetti P, Bero L (2009).Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation: *PLOS Medicine*. http://www.biomedcentral.com/1471-244X/8/3
2. Gobburu JVS, Lesko LJ (2009).Quantitative Disease, Drug, and Trial Models. *Annual Review of Pharmacology and Toxicology*. 49: 291-301.
3. Chow SC, Liu JP (2004). Design and Analysis of Clinical Trials*:* Concept and Methodologies. John Willey and Sons.
4. Huff TE (2003). The Rise of Early Modern Science: Islam, China, and the West.
5. Lipkovich I, Adams DH, Mallinckrodt C, Faries D, Baron D, Houston JP (2008). Evaluating Dose Response from flexible Dose Clinical Trials. *BMC Psychiatry*.
6. Pocock SJ (2004). Clinical Trials. A Practical Approach. John Wiley & Sons.
7. Gebski V, Beller E, Keech AC (2001). *Randomized Trials: Elements of a Good Study*. *Medical Journal of Australia*. 175: 272-274. Cambridge University Press. p. 218
8. Koren G, Boloja M, Long D, Feldman Y, Shear NH (1998). Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *Am J Obstet Gynecol.* 160:1190-4.
9. Dally A, Thalidomide (1998). Was the tragedy preventable? *Lancet*.351:1197-1199
10. Koren G. Pastuszak A (1990). Prevention of unnecessary pregnancy termination by counselling women on drug, chemical and radiation exposure during the first trimester. *Teratology*. 41: 657-61.
11. Koren G, Pastuszak A, Sinya I (1998). Drugs in pregnancy. *N Engl J Med*. 338(16): 1128-1137.
12. Collier R (2009). Drug development cost estimates hard to swallow. *CMAJ*. February 3; 180(3): 279–280

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Acute Kidney Injury and Massive Proteinuria Secondary to Epstein - Barr Virus - Associated Nephrotic Syndrome

By Awad Magbri, MD, FACP & Thanh G Nguyen, MD
Partners in Nephrology and Endocrinology, United States

The Case- The case is that of 69 year old female who went on vacation and fell on her knees. She noticed progressive swelling of both legs over 2 weeks duration. During this period she gained 44 pounds in weight. She presented with sudden onset of edema of the lower extremity and weigh gain. She had 16 g/day of proteinuria. Past medical history is significant of hypertension of unknown duration. She had never seen a doctor in the last year. Her laboratory data showed 30 grams protein in 24 hrs urine, and her serum creatinine was 1.7 mg/dl. The baseline serum creatinine was not known.

Keywords: epstein virus infection, interstitial nephritis, minimal change disease, nephrotic syndrome, proteinuria, acute renal failure.

GJMR-F Classification: NLMC Code: WJ343

Strictly as per the compliance and regulations of:

© 2016. Awad Magbri, MD, FACP & Thanh G Nguyen, MD. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/ 3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Acute Kidney Injury and Massive Proteinuria Secondary to Epstein - Barr Virus - Associated Nephrotic Syndrome

Awad Magbri, MD, FACP [α] & Thanh G Nguyen, MD [σ]

Keywords: epstein virus infection, interstitial nephritis, minimal change disease, nephrotic syndrome, proteinuria, acute renal failure.

I. The Case

The case is that of 69 year old female who went on vacation and fell on her knees. She noticed progressive swelling of both legs over 2 weeks duration. During this period she gained 44 pounds in weight. She presented with sudden onset of edema of the lower extremity and weigh gain. She had 16 g/day of proteinuria. Past medical history is significant of hypertension of unknown duration. She had never seen a doctor in the last year. Her laboratory data showed 30 grams protein in 24 hrs urine, and her serum creatinine was 1.7 mg/dl. The baseline serum creatinine was not known.

Her laboratory showed negative ANA, ANCA, and normal complement levels. No monoclonal gamopathy were detected on serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP). EBV titers came back IgM 1.68 (high), IgG 2.81 (high), EBV nuclear antigen IgG 3.11 (high). Laboratory interpretation of the results is that of recent EBV infection or reactivation.

Her renal biopsy findings revealed:

1. Early equivocal "Tip" lesion involving 1-2 of 25 glomeruli. Non-globally sclerotic glomeruli
2. Extensive podocyte foot process fusion on ultra-structural examination.
3. Isometric tubular vacuolization suggestive of acute tubular injury with protein reabsorption granules in the tubular epithelial cells.
4. Chronic renal changes (5/30; 17%) glomeruli are globally sclerotic.
5. Moderate hypertensive arterial nephrosclerosis.
6. Mild interstitial fibrosis and tubular atrophy.
7. Minimal interstitial lymphocytic inflammation
8. Immunofluorescent and ultrastrucural examination are negative for selective specific immune/electron-dense deposits. However, the EM showed widespread podocyte foot process fusion (>90%) consistent with the high level of proteinuria possibly secondary to minimal change disease/tip lesion FSGS.

Author α σ: Dialysis Access Center of Pittsburgh, PA & UPMC-St Margaret Hospital, Pittsburgh, PA. e-mail: elmagbri@hotmail.com

II. Case Discussion

Infection with Epstein-Barr virus is ubiquitous in adults and it is estimated that over 95% of adults worldwide is infected with the virus (1). It causes infectious mononucleosis (IM) in the acute phase. Most patients recover without sequelae, however, acute complications are associated with EBV infection.

Sub-clinical renal involvement is not uncommon in EBV infection; 16% of patients with IM infection have abnormalities in urinary sediment (2). Immune complex glomerulonephritis in the form of minimal change disease or membranous glomerulopathies are the most common renal presentation of EBV infection. Acute renal failure and cholemic nephrosis are rare but can also occur (2,3).

Acute kidney injury in adults with minimal change disease has been reported in approximately 25-35% of adults. It is mainly presented at the time of nephrotic syndrome (4-9). However, Patients who develop AKI are more likely to be older, male, hypertensive, and have severe proteinuria. These features are present in our patient except for the gender. AKI occurred in 25% (24/95) patients with MCD in the United States (6). In 7 patients, it occurred in a relapse of MCD. However, in 17/95 the AKI occurred concurrently with the onset of MCD. Patients with AKI are older with hypertension. In these patients proteinuria was higher, and hypoalbuminemia and edema were severe (4). AKI was relentless in these patients; and most patients were oliguric at the time of presentation. It is noteworthy, that 20% of these patients required renal replacement therapy. Acute tubular necrosis was the underlying cause of AKI in these patients (4-6, 7,9).

Meyer et al and others (10) reported that 18% of patients with AKI associated with MCD are due to rahbdomyolysis and myoglobuinuria. Two of his patients had MCD and 10/27 patients had acute interstitial nephritis. However, Mayer et al failed to identify EBV RNA in the renal biopsy tissue and instead suggested that the EBV antigens in infiltrating lymphocytes activated a massive T-cell mediated immune response. In contrast, Bao (11) and Cataudella's (12) analysis

© 2016 Global Journals Inc. (US)

reported detection of the EBV genome using polymerase chain reaction (PCR) technique in renal samples. EBV DNA has since been found in biopsies of patients with IgA nephropathy and membranous nephropathy as well.

The pathogenesis of AKI in EBV infection remains unclear but activation of the T-lymphocytes may be directly involved in EBV renal injury (2). Bao et al (11) demonstrated a predominance of cytotoxic T-cells in the interstitium with evidence of EBV DNA detected with PCR in renal tissue in patients with interstitial nephritis. EBV receptors (CD21) were detected in the proximal tubular cells and were up-regulated in the EBV infected tissues (12).

Okada et al, in 2002 (13) reported a case of chronic active EBV infection who developed both acute interstitial nephritis and MCD. Renal biopsy of this case showed tubular epithelial atypia and lymphocytic interstitial infiltrates. EBV DNA was also detected with PCR in some infiltrating lymphocytes.

There is no strong current literature on the use of steroids in IM. However, Mikhalkova et al treated a case of MCD associated with EBV infection with steroids with rapid and complete response of the MCD (14), however, anecdotal reports claim its effectiveness in MCD.

In conclusion, MCD is rarely reported renal complication of EBV infection with few cases reported in the literature. It is exquisitely response to steroids. EBV infection should be considered in all cases of heavy proteinuria with LM, IF, EM features of MCD especially if the onset of MCD is preceded by viral prodromal illness.

References Références Referencias

1. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med 2010; 362: 1993-2000.
2. Dylewski JM, Roy IM, Eid JM. Acute renal failure associated with acute Epistein-Barr virus infection. Infect Dis Clin Pract 2008; 16: 127-128
3. Bredewold OW, de Fijter JW, Rabelink T. A case of mononucleosis infection presenting with cholemic nephrosis. NTD Plus 2011; 4: 3.
4. Smith JD, Hayslett JP. Reversible renal failure in the nephrotic syndrome. Am J Kidney Dis 1992; 19: 201.
5. Jennette JC, Falk RJ. Adult minimal change glomerulopathy with acute renal failure. Am J Kidney Dis. 1990; 16: 432.
6. Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. Clin J Am Soc Nephrol. 2007; 2: 445.
7. Chen T, Lv Y, Lin F, Zhu J. Acute kidney injury in adult idiopathic nephrotic syndrome. Ren Fail 2011; 33: 144.
8. Chen CL, Fang HC, Chou KJ, et al. Increased endothelin 1 expression in adult-onset minimal change nephropathy with acute renal failure. Am J Kidney Dis. 2005; 45: 818.
9. Esparza AR, Khan SI, Garella S, Abuelo JG. Spectrum of acute renal failure in nephrotic syndrome with minimal (or minor) glomerular lesions. Role of hemodynamic factors. Lab Invest 1981; 45: 510.
10. Mayer HB, Wanke CA, Williams M, et al. Epistein-Barr virus-induced infectious mononucleaosis complicated by acute renal failure: case report and review. Clin Infect Dis 1996; 22: 1009-1018.
11. Bao L, Zhang Y, Zheng X. Detection of Epistein-Barr virus DNA in renal tissue from patients with interstitial nephritis. Zhonghua Nei Ke Za Zhi. 1996; 35: 542-544.
12. Cataudella JA, Young ID, Illiescu EA. Epistein-Barr virus-associated acute interstitial nephritis: infection on immunologic phenomenon? Nephron 2002: 92: 437-439.
13. Okada H, Ikeda N, Kobayashi T, et al. An atypical pattern of Epistein-Barr virus infection in a case with idiopathic tubu-interstitial nephritis. Nephron 2002; 92: 440-444.
14. Mikhalkova D, Khanna S, Vaidya R, Seth S, Hogan MC. Epistein-Barr virus-associated nephrotic syndrome. Clin Kidney J 2012; 5: 50-52.

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Childhood Hypocalcemia: The Aetiological Pattern

By Nasir A. M. Al Jurayyan, MD
King Saud University

Abstract- *Background:* Hypocalcemia is not that rare condition and could be a potentially life threatening. Identifying the etiology is important for successful management.

Results: A total of 60 patients were seen in the period under review, December 1989 and June 2016, with childhood hypocalcemia. Twenty-seven (45.0%) patients were parathyroid hormone deficient, while rickets diagnosed in 25 (41.7%) patients.

Design and setting: A retrospective, hospital based study was conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia during the period December 1989 and June 2016.

Materials and Methods: Medical records of children beyond the neonatal period with hypocalcemia were reviewed for aetiological diagnosis. Detailed history, clinical manifestation, and results of all the laboratory, and radiological investigations were obtained.

Conclusion: This study showed that parathyroid hormone (PTH) deficiency (45%) and rickets (41.7%) were the most common causes of childhood hypocalcemia.

Keywords: *aetiology, childhood, hypocalcemia.*

GJMR-F Classification: *NLMC Code: WK140*

Strictly as per the compliance and regulations of:

© 2016. Nasir A. M. Al Jurayyan, MD. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/ 3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Childhood Hypocalcemia: The Aetiological Pattern

Nasir A. M. Al Jurayyan, MD

Abstract- Background: Hypocalcemia is not that rare condition and could be a potentially life threatening. Identifying the etiology is important for successful management.

Design and setting: A retrospective, hospital based study was conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia during the period December 1989 and June 2016.

Materials and Methods: Medical records of children beyond the neonatal period with hypocalcemia were reviewed for aetiological diagnosis. Detailed history, clinical manifestation, and results of all the laboratory, and radiological investigations were obtained.

Results: A total of 60 patients were seen in the period under review, December 1989 and June 2016, with childhood hypocalcemia. Twenty-seven (45.0%) patients were parathyroid hormone deficient, while rickets diagnosed in 25 (41.7%) patients.

Conclusion: This study showed that parathyroid hormone (PTH) deficiency (45%) and rickets (41.7%) were the most common causes of childhood hypocalcemia.

Keywords: aetiology, childhood, hypocalcemia.

I. Introduction

Hypocalcemia is a potentially life-threatening metabolic disturbance. It can result in severe symptoms that require rapid management. Hypocalcemia occurs most commonly as a result of deficiency of parathyroid hormone (PTH). Though, there are many other potential etiologies of hypocalcemia, one usually does not consider them seriously unless the most common cause is ruled out or unless the initial evaluation suggest another cause is likely.

In primary hypoparathyroid, an assay that measures intact circulating PTH will be low, while in virtually all other causes associated with hypocalcemia. PTH levels are elevated.[1-4]

This article focuses upon the etiology of hypocalcemia beyond the neonatal period, seen in a major teaching hospital, King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia over three decades, December 1989 to July 2016.

Then KKUH is the main teaching hospital of the King Saud University (KSU) and considered as one of the major referral hospitals in the region, and provides primary, secondary, and tertiary health care services for the local population and also receives patients referred from all over the country.

Author: Professor and Senior Consultant Endocrinologist, Endocrine Division, Department of Pediatrics, College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, Saud Arabia.
e-mail: njurayyan@gmail.com

II. Materials & Methods

During the period under review, December 1989 to June 2016, all patients who were diagnosed, beyond the neonatal period to have hypocalcemia were retrospectively reviewed. Detailed history, clinical manifestations and results of all the laboaratory, radiological and ancillary investigations were obtained. The aetiological diagnosis was based on specific investigations as recommended.

III. Results

During the period under review, December 1989 and June 2016, a total of 60 patients beyond neonatal period were seen by the author in the pediatric endocrine service, King Khalid University Hospital, Riyadh, Saudi Arabia. Table, showed the aetiological diagnosis of the group. In 27 (45.0%) patients, parathyroid hormone (PTH) deficiency was found while rickets was the diagnosis in 25 (41.7%) patients. Celiac disease was diagnosed in 6 (10.0%) patients.

IV. Discussion

Hypocalcemia beyond neonatal period is not that rare. It varies from an asymptomatic biochemical abnormality to a life threatening conditions, depending on the duration, severity and rapidity of development. Hypocalcemia is caused by loss of calcium into circulation. In a community with high prevalence of consanguinity mating and increased incidence of autosomal disorders,[5,6] various forms of hypoparathyroidism exist and constitute the major cause. Simple hypoparathyridism usually occurs sporadically, though an autosomal dominant pattern of inheritance has been reported. In most cases the pathogenesis is unknown, but agenesis, partial or complete atrophy, and inflammatory damage of the parathyroid glands are possible mechanisms. However the diagnosis of isolated hypoparathyroidism cannot be made with certainty in childhood, since children who first appears to have this disorder often develop additional endocrine or immunological abnormalities later on.[7-9]

Damage to the parathyroid glands is a well-established risk of neck surgery, especially during total or subtotal thyroidectomy. Permanent parathyroid

© 2016 Global Journals Inc. (US)

deficiency occurs in about five to ten percent of subtotal thyroidectomies and is significantly more common after total thyroidectomy for malignant thyroid disease. Hypoparathyroidism is usually caused by an interference with the blood supply of the glands and is rarely due to complete ablation of the parathyroid tissue. Non-surgical damage to the parathyroid glands can occur as a result of massive doses of external irralation. However, the parathyroids are relatively radiation resistant so definite hypoparathyroidism following treatment for thyroid disease is exceptionally rare.

A well-established relationship exists between magnesium and calcium homeostasis. Magnesium deficiency may lead to hypocalcemia by either PTH synthesis or release and end-organ, bone, refractoriness to the effects of PTH.(11)

Rickets was the second most common cause of hypocalcemia in our study. The various forms shown in table. The clinical and radiological is highly variable, depending on the age, the etiology and the duration and severity of the disorder.(3,4,12-15) Vitamin D deficiency was common, however, derangement in Vitamin D metabolites or action is not that rare.

Celiac disease should be considered in patients with hypocalcemia of unknown etiology, especially because gastrointestinal symptoms may be absent or mild. Six (10%) patientsin our series were diagnosed to have celiac disease.(16)

In conclusion, this study showed that parathyroid hormone (PTH) deficiency (45%) and rickets (41.7%) were the most common causes of childhood hypocalcemia

V. Acknowledgement

The author would like to thank Mrs. Cecile M. Sael for typing the manuscript, and extends her thanks and appreciations to Miss Hadeel N Aljurayyanfor her help and support.

Conflict of Interest

The author have no conflict of interest to declare.

References Références Referencias

1. Thakker RV; Parathyroid disorders and diseases altering calcium metabolism. In Worrall D, Cox T, Firan J, Benz E, eds oxford textbook of medicine, 4th ed. oxford: Oxford University press 2003.
2. Pettifor JM.; Nutritional and drug induced rickets and osteomalacia. In Favus MJ ed. Nutritional and induced rickets and osteomalacia: Primer on the metabolic and bone disorders and disorders of bone metabolism. 5th ed. Washington DC. American Society for Bone Mineral and research 2006; 330-338.
3. Wharton B, Bishop N. Rickets Lancet 2003; 362: 1389-140.
4. Holick MF; Vitamin D deficiency,NEngl J Med 2007; 357: 266-81.
5. Al Jurayyan NAM, Osman HA,; The increased prevalence of Congenital adrenal hyperplasia: The roles of consanguinity and multiple siblings involvement. Eur J Res in Med Sci 2015; 3(1): 31-34
6. Saedi- Wong S, Al Frayh AR, Wong HYM; Socio – economic epidemiology of consanguineous mating's in Saudi Arabian population J Asian Afri stud 1989; 24: 247-252
7. Shoback D; Clinical practice, hypoparathyroidism N Eng J Med 2008; 359: 391-403
8. Marx SJ; Hypoparathyroidism and hyperperi-thyrodism disorders, N Engl J Med 2000; 343: 1863-75
9. Al Ali AO, Al Ayed OA, Al IssaSD,AlJurayyan AN, AL Jurayyan NA; Autoimmune polyendocrine Syndrome type I, Int J recent Sci Res 2015; 6(7);5058-5061
10. Sanjad SA, Sakati NA, Abu Osba YK, Kaddoura R, Milner RD; A new Syndrome of Congenital hypoparathyroidism, severe growth failure and dysmorphicfeatures , Arch Dischild 1991; 66, 193-196
11. Anast CS, Winnacker JL Forte LR, Burns TW; Impaired release of parathyroid hormone in magnesium deficiency, J clin Endocrine Metab 1976, 42, 707-17.
12. Al Jurayyan NA, Mohamed S, Al Issa SD, Al Jurayyan AZ N; Rickets and osteomalacia in Saudi children and adolescents attending endocrine clinic, Riyadh Saudi Arabia. Sudan J Pediatric 2012; 12(1): 56-63.
13. Miller WL, Anthony AP; Genetic disorders of Vitamin D biosynthesis, EndocrinolMetabClin N Am 1999; 28; 825-840.
14. Linglart A, Bastepe M, Lupponer HSimilar clinical and laboratory findings in patients with symptomatic autosomal dominant and sporadic pseudohy-poparathyroidism type 1b despite different epigenetic changes at GNAS locus. Clinic Endocrinol 2007; 67: 833-31.
15. Al Jurayyan NA, Mohammed S, Saad-Uddin MF, Al Jurayyan AZ N; Pseudohypoparathyroidism type 1b: A rare cause of femoral neck fracture J Taiba university Med Sci 2011, 6(1): 42-46.
16. Al Jurayyan AZN, AL Otaibi AM, Al Jurayyan RN, AL Assiri AM, AL Jurayyan NA,Celiac disease presenting as rickets in children, Pediatrics me 2009; 14(3), 68-70.

© 2016 Global Journals Inc. (US)

Table 1: Aetiology of childhood hypocalcemia in 60 patients

	Diagnosis	Number	(%)
Parathyroid hormone (PTH) deficiency (45%)	• Isolated hypoparathyroidism	10	16.67
	• Hypoparathyroidism associated with Sanjad-Sakatisyndome	6	10.00
	• Hypoparathyroidism associated with autoimmune polyendocrine syndrome	7	11.67
	• Post-thyroidectomy	2	3.33
	• Hypomagnesium	2	3.33
Rickets (41.7%)	• Nutritional rickets	13	21.67
	• Anti-convulsant induced rickets	4	6.67
	• Vitamin D dependent rickets Type 2	5	8.33
	• Hypophosphotemic Rickets	2	3.33
	• Pseudo hypo-hypo-parathyroidism type 1b	1	1.67
Miscellaneous (13.3%)	• Celiac disease	6	10.0
	• Chronic renal failure	2	3.33
TOTAL		60	100

© 2016 Global Journals Inc. (US)

This page is intentionally left blank

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Erlotinib Induced Fatal Interstitial Lung Disease: An Underreported Toxicity

By Ramy Sedhom, Elan Gorshein, Jane Date Hon, Judith Amorosa & Serena Wong

Rutgers Robert Wood Johnson Medical School, United States

Abstract- Lung cancer is the leading cause of cancer-related mortality around the world, with 85% of cases identified as non-small-cell lung cancer (NSCLC). Adenocarcinoma is the most common histologic subtype in the US and accounts for more than 50% of all NSCLC. Activating mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase are found in approximately 15% of NSCLC adenocarcinoma in the US (and up to 62% in Asia) and is more common in nonsmokers. The presence of such a mutation is associated with a more favorable prognosis and predicts for sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and afatinib. Treatment is well tolerated, with mild common adverse side effects of skin rash and diarrhea. However, increased experience with the use of these drugs has led to reports of rare serious adverse effects such as interstitial lung disease.

Keywords: erlotinib, Interstitial lung disease, Rare Side effects, chemotherapy.

GJMR-F Classification: NLMC Code: WF600

Strictly as per the compliance and regulations of:

© 2016. Ramy Sedhom, Elan Gorshein, Jane Date Hon, Judith Amorosa & Serena Wong. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/ 3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Erlotinib Induced Fatal Interstitial Lung Disease: An Underreported Toxicity

Ramy Sedhom [α], Elan Gorshein [σ], Jane Date Hon [ρ], Judith Amorosa [ω] & Serena Wong [¥]

Abstract- **Lung cancer is the leading cause of cancer-related mortality around the world, with 85% of cases identified as non-small-cell lung cancer (NSCLC). Adenocarcinoma is the most common histologic subtype in the US and accounts for more than 50% of all NSCLC. Activating mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase are found in approximately 15% of NSCLC adenocarcinoma in the US (and up to 62% in Asia) and is more common in nonsmokers. The presence of such a mutation is associated with a more favorable prognosis and predicts for sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and afatinib. Treatment is well tolerated, with mild common adverse side effects of skin rash and diarrhea. However, increased experience with the use of these drugs has led to reports of rare serious adverse effects such as interstitial lung disease.**

Keywords: erlotinib, Interstitial lung disease, Rare Side effects, chemotherapy.

I. Introduction

Lung cancer is the leading cause of cancer-related mortality around the world, with 85% of cases identified as non-small-cell lung cancer (NSCLC)[1.] The epidermal growth factor receptor (EGFR) signaling pathway plays a crucial role in regulating tumor growth and survival and is important in the progression of NSCLC[2]. The signaling pathway of EGFR is estimating to be activated in more than half of patients with NSCLC, increasing the role of targeted therapy. [3]Two reversible EGFR tyrosine kinase inhibitors (EGFR-TKIs), gefitinib and erlotinib, are often used therapies in EGFR-mutated NSCLC and are approved by the US Food and Drug Administration[4, 5]. They are also approved for treatment of carcinomas of the pancreas that are locally advanced. Treatment is often well tolerated, with mild common adverse side effects of skin rash and diarrhea. [6] However, growing incidence of major adverse side effects, such as interstitial lung disease (ILD), continues to be reported since drug approval[7,8]. Though the mechanism of adverse-pulmonary events is not completely understood, careful recognition and documentation of both incidence and risk of ILD is important to allow early recognition of potential toxicity.We report a histologically confirmed case of fatal interstitial pneumonitis, with acute lung injury, associated with erlotinib therapy.

II. Case Report

A 68-year old female, non-smoker, with obstructive sleep apnea requiring bi-level positive airway pressure, chronic obstructive lung disease, and non-insulin dependent diabetes mellitus was diagnosed with metastatic adenocarcinoma of the lung (to left humerus and thyroid). She initially presented with a 10-year history of asymptomatic hypercalcemia for which imaging of the parathyroid gland was performed and incidentally showed several abnormal lung masses. Subsequent staging scans showed a large hilar mass as well as a large mass in the left lower lobe, several metastatic lesions in the left lung, and a lytic lesion in the left humerus (Figure 1,2). She underwent VATS with wedge resection of the lung nodules for diagnostic purposes. Pathology showed poorly differentiated adenocarcinoma and genomic testing revealed a mutation in EGFR. She completed a short course of palliative radiation therapy to the primary tumor in the lung to prevent bronchial compression as well as to the humerus for pain control. She initiated systemic therapy with erlotinib 150mg PO daily, which she started midway through her RT course.

Two weeks following the beginning Erlotinib treatment (4 weeks following radiation therapy), she reported a dry cough and dyspnea on exertion. Her pulse ox dropped to 92% after ambulation. A CT scan showed smaller masses and scarring in the left lower lobe in the area of surgery (Figure 3).

Approximately one month later, she reported increased SOB without hemoptysis, fevers, or chills. She was treated with a prednisone taper, initial dose of 60mg daily. The patient transiently responded well. However, upon lowering the daily dose to 40 mg her symptoms worsened, and a 60 mg dose was resumed. Repeat CT scan showed smaller masses, but new left lung infiltrates and an area of consolidation in the left lung that vaguely outlined the radiation port. There was an associated left pleural effusion (Figure 4). Follow-up visit showed resting oxygen level of 88%. She was prescribed home oxygen therapy and levofloxacin for

Author α: Department of Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.
e-mail: sedhomr@gmail.com
Author σ ¥: Division of Hematology & Oncology, Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.
Author ρ: Department of Pathology and Laboratory Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.
Author ω: Department of Radiology, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.

© 2016 Global Journals Inc. (US)

bilateral pneumonia. Despite the initiation of antibiotics and steroids, the patient reported worsening of her symptoms, with SOB at rest, persistent cough, and new onset fevers and chills. She was admitted to the hospital.

On admission, vital signs were significant for a temperature of 100.4 F, heart rate of 116, respiratory rate of 16, and oxygen saturation of 70%. Blood gas showed pH 7.48, pCO2 28 mmHg, pO2 <44mgHg, O2 saturation 75.4%. Labs included hemoglobin 11.7 g/dl, WBC 17.5 thousand/uL with left shift. Her creatinine was at baseline. CTA of the chest was negative for pulmonary embolus, but noted significantly worsened airspace opacities bilaterally when compared with prior films. Patient was placed on broad-spectrum antibiotics and transitioned to prednisone 40 mg twice daily. Blood cultures revealed no organisms. Follow-up chest x-ray demonstrated diffuse bilateral infiltrates and pulmonary edema. Echocardiogram was unremarkable for a cardiac etiology of her symptoms. On day three of admission, patient required intubation for respiratory distress and vasopressor therapy for hypotension.

A bronchoscopy was performed. Bronchial washing was negative for diffuse alveolar hemorrhage. New labs revealed hyponatremia. Respiratory viral panel, Cytomegalovirus, Pneumocystis, Legionella and other infectious testing were negative. Her respiratory distress increased and steroids were thus increased to 60mg every six hours. Despite maximal medical and ventilatory support, the patient continued to deteriorate rapidly with increased oxygen requirements and worsening hypoxemia. Repeat CT chest revealed bilateral, diffuse pneumomediastinum with posterior displacement of the heart, and worsening airspaces, sparing the apices (Figure 5). Patient's condition deteriorated so she was transitioned to comfort care and expired.

A limited autopsy of the lungs was performed. Gross examination revealed pale lungs with cobblestoning. Microscopic examination (Figure 6) showed varying stages of diffuse alveolar damage (DAD).The right lung exhibited diffuse, early to acute organizing proliferative DAD. The left lung exhibited acute organized proliferative DAD, with end-stage DAD over the left lower lobe. There was no evidence of residual tumor. These findings led to a clinical diagnosis of interstitial pneumonitis due to erlotinib treatment, likely superimposed with radiation pneumonitis. The different stages of DAD within various lobes of the lung, with severe honeycombing over the irradiated lobe suggest interstitial pneumonitis as a complication of erlotinib treatment in the setting of overlying radiation pneumonitis.

III. Discussion

New cancer therapies are quickly emerging, with promising, effective treatments for many patients. Erlotinib received FDA approval in 2004 as monotherapy for locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In the original FDA Drug Approval summary, ILD was observed during treatment in 0.8% of patients; similar to the placebo incidence.[3] The EGFR-TKIs are thought to be relatively safe therapies in the treatment of patients with advanced NSCLC. Although reported with a relatively low incidence ranging from 3.5-5%, ILD is a growing concern as a significant, sometimes fatal adverse side effect.[9] It is particularly important to highlight the risk and incidence of ILD as EGFR-TKIs are increasingly used in daily practice, both for their efficacy and tolerability. Identifying patients at high risk of ILD important to reduce occurrence. Unfortunately, there are currently no guidelines for treatment as randomized controlled studies investigating the issue are lacking. For now, providers are suggested to discontinue treatment in patients with known ILD.[3-4]

Assessment of ILD is particularly challenging, as it is not a single disease entity, but a spectrum of lung pathology. In addition, patients with NSCLC often have confounding factors, such as heart failure, pulmonary infectious disease, and/or disease progression within the lungs. In addition, the pathophysiology of drug-induced injury is not well understood. Some have suggested that EGFR inhibitors interfere with the repair process of pulmonary tissue, as epidermal growth factor is secreted onto bronchial surface fluid by pneumocytes. The primary damage is thought to occur due by immunocyte activation, likely modulated by a number of host and environmental factors. [10] Certainly, more studies are needed to understand the disease process.

Drug associated ILD appears to be higher among Japanese patients than Caucasian patients for reasons unclear.[4] No study has yet examined the relationship between constitutional or environmental factors specific to Japanese Patients. ILD related to drug therapy requires high suspicion and exclusion of other potential causes.

Common histopathologic studies reveal alveolar edema, pneumocyte hyperplasia, the accumulation of fibrin, and formation of hyaline membranes. Of note, these findings are not pathognomonic, as they are also seen in acute-respiratory distress syndrome and acute interstitial pneumonitis.[11] The time range between drug administration and symptom presentation is highly variable, ranging from 2-282 days. [12] Diffuse alveolar damage (DAD) is a progressive process that goes through several stages. The early acute stage exhibits edema and hyaline membrane formation over the alveolar cells. Subtle interstitial fibrosis may be seen. The early stage develops within the first 1-2 weeks. With progression, the organizing fibroproliferative stage develops. Hyaline membranes are being actively resorbed, and fibroblasts migrate into the interstitium.

© 2016 Global Journals Inc. (US)

Fibrin thrombi are seen within the vessels. There is acute inflammation, squamous metaplasia, and type 2 pneumocytes proliferate to replace the damaged alveolar cells.[13] As the disease process progresses, end stage DAD ensues, characterized by increased squamous metaplasia, marked fibroblastic proliferation, bronchiolar dilatation, and severe fibrosis of the interstitium. The end result is a solid honeycombed appearance of the lung. Clinically, patients present with dyspnea and cough, and as the disease progresses, work of breathing is increased and patients eventually develop respiratory failure, as seen in the case presented. Radiographically, there are non-specific changes, manifested by edema and diffuse, infiltrative opacities of the lung. Treatment is with corticosteroids and supportive care. Definitive treatment is with lung transplant. [14, 15]

Diffuse alveolar damage may be instigated by different factors, and a thorough history is required to find causal source. Acute radiation pneumonitis affects 10% of patients who undergo radiation therapy. Clinical manifestation is usually evident 1-6 months after radiation treatment. X-rays show diffuse chest infiltrates over the area of the radiation portal. While this may spread to non-irradiated areas of the lung, bilateral involvement is rare.[16] Erlotinib and radiation may have a synergistic effect, increasing the incidence of interstitial pneumonitis in patients treated with both. A study of patients who developed interstitial pneumonitis with concurrent treatment with radiation therapy and erlotinib showed the pneumonitis could not be reversed with methylprednisone.[17]

Identifying at-risk patients is a major concern that warrants further investigation. At this point, more is known regarding potential risk factors for gefitinib. A retrospective survey of the prevalence and risk factors for gefitinib-induced ILD in Japan found ILD to be significantly associated with male gender, prior smoking history, and concomitant interstitial pneumonia. Prior chemotherapy and radiation to the lungswas also reported as a predisposition to ILD.[18] Whether these findings are also correlated with erlotinib is yet to be studied.

Patients on erlotinib often have already received treatment with other antineoplastic agents. Pulmonary toxicity, ranging from interstitial pneumonitis to acute respiratory syndrome, is not an uncommon side effect of chemotherapy, as it has been described for gemcitabine[19], mitomycin[20], vinorelbine tartrate[21], docetaxel[22], ifosfamide[23]. Lung injury occurs usually early after administration of chemotherapy. Whether erlotinib itself contributes to lung toxicity due to its own unique chemical properties or rather exacerbatespre-existing pulmonary toxicity from prior chemotherapy or radiation is yet clarified.

To date, pre-existing pulmonary disease is not an absolute contraindication to treatment with erolitinib. Given the growing number of reported pulmonary toxicities, the authors recommend documenting baseline respiratory status and symptoms prior to the initiation of medication. This would allow objective monitoring of subtle changes after initiation of drug therapy.

Limitations at this time are extended to management of erlotinib associated lung toxicity. Case reports show varied success with high dose corticosteroid therapy. Though many patients seem to have responded to supportive therapy (including high dose supplemental oxygen and mechanical ventilation when necessary), many patients have died due to progressive respiratory failure, as seen with the patient whose story is described above. In addition, follow-up is limited when evaluating for recurrence of pulmonary disease in those with him authors have described success.

In conclusion, as demonstrated, EGFR-TKIs carry the substantial risk of developing ILD in patients with advanced NSCLC, although infrequently. Awareness of the potential for lung toxicity is necessary. Erlotinib should be considered among the antineoplastic agents with the potential to contribute to pulmonary disease. Physicians are encouraged to evaluate new or worsening pulmonary symptoms in patients receiving EGFR-TKI therapy. Further studies are needed to better elucidate risk factors, disease pathophysiology, and potential treatments to lower the incidence and mortality of ILD associated with EGFR-TKIs.

[1] Jemal A, Seigel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clini. 2010; 60 (5): 277-300.

[2] Scaltriti M, Baselga J. The epidermal growth factor receptor pathway: a model for targeted therapy. Clin Cancer Res. 2006; 12 (18): 5268-5272.

[3] Herbst R, Heymach J, Lippman S. Lung cancer. NEJM 2008; 358: 1367-80.

[4] Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval summary: erlotinib (Tarceva) tablets. Oncologist. 2005; 10(7): 461-6.

[5] Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD Jr., Morse D, et al. United States Food and Drug Administration Drug Approval summary: gemfitinib (ZD1839: Iressa) tablets. Clin Cancer Res. 2004; 10(4): 1212-8.

[6] Qi WX, Tang LN, He AN, Yao Y, Shen Z. Incidence and risk of treatment-related mortality in cancer patients treated with EGFR-TKIs: A meta-analysis of 22 phase III randomized controlled trials. Respir Med. 2013; 107(8): 1280-3.

[7] Nasrallah H, Bar-Sela G, Haim N. Fatal interstitial lung disease associated with gemcitabine and ertolinib therapy for lung cancer. Med Oncol. 2012; 29 (1): 212-4.

[8] Tammaro KA, Baldwin PD, Lundberg AS.Interstitial lung disease following erlotinib (Tarceva) in a patient who previously tolerated gefitinib (Iressa). J Oncol Pharm Pract. 2005; 11(3): 127-30.

[9] Hotta K, Kiura K, Takigawa N, Yoshioka H, Harita S, Kuyama S, et al. Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese Patients with non-small cell lung cancer: the Okayama Lung Cancer Study Group experience. J Thorac Oncology. 2010; 5 (2): 179-184.

[10] Aida S, Tamai S, Sekiguchi S, Shimizu N. Distribution of epidermal growth factor and epidermal growth factor receptor in human lung: immunohistochemical and immunoelectronmicroscopic studies. Respiration. 1994; 61 (3):161-6.

© 2016 Global Journals Inc. (US)

[11] Liu V, White DA, Zakowski MF, Travis W, Kris MG, Ginsberg MS, Miller VA, Azzoli CG. Pulmonary toxicity associated with erlotinib. Chest 2007; 132: 1042-4.
[12] Peerzada M, Spiro T, Daw H. Pulmonary Toxicities of Tyrosine Kinase Inhibitors. Clin Advan Hem and Onc 2011: 9 (11): 824-836.
[13] Chou CI, KO H, Wang C, Yu C, Kuo H, Huand C. Erlotinib-associated near fatal interstitial pneumonitis in a patient with relapsed lung adenocarcinoma. Chang Guand Med J. January-february 2010; 33 (1): 100-105.
[14] Katzenstein, A. Katzenstein and Askin's Surgical Pathology of Non-neoplastic Lung Disease, 4th edition.2006; Elsevier, Inc. Philadelphia, PA; 32-33.
[15] Ren, S, Li Y, Li W, Zhao Z, Jin C, Zhang D, Fatal assymetric interstitial lung disease after erlotinib for lung cancer. Respiration. 2012; 84 (5): 431-435.
[16] Yamashita H, Takahashi W, Haga A, Nakagawa K. Radiation pneumonitis after sterotactic radiation therapy for lung cancer. World J Radiol.2014; 6 (9); 708-715.
[17] Zhang H, Hou H, Yuan Z, Wang J, Pang Q, Zhao L, Wang P: Preliminary analysis of the risk factors for radiation pneumonitis in patients with non-small-cell lung cancer treated with concurrent erlotinib and thoracic radiotherapy. Onco Targets Ther. 2014; 7: 807-813.
[18] Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, Ariyoshi Y, Fukuoka M. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small cell lung cancer patients treated with gefitinib. J Clin Onc 2006: 24: 2549-5.
[19] Pavlakis N, Bell D, Millward M, Levi J; Fatal pulmonary toxicity resulting from treatment with gemcitabine. Cancer 1997, 80: 286-291.
[20] Orwoll E, Keissling P, Patterson J: Interstitial pneumonia from mitomycin. Ann Int Med 1978:, 89: 352-355.
[21] Kouroukis C, Hings I: Respiratory Failure following vinorelbine tartrate infusion in a patient with non-small cell lung cancer. Chest 1997, 112: 846-848.
[22] Read WL, Mortimer JE, Picus J: Severe Interstitial Pneumonitis Associated with Docetaxel Administration. Cancer 2002, 94: 847-853.
[23] Baker W, Fistel S, Jones R, Weiss R: Interstitial pneumonitis associated with ifosfamide therapy. Cancer 1990, 65: 2217-2221.

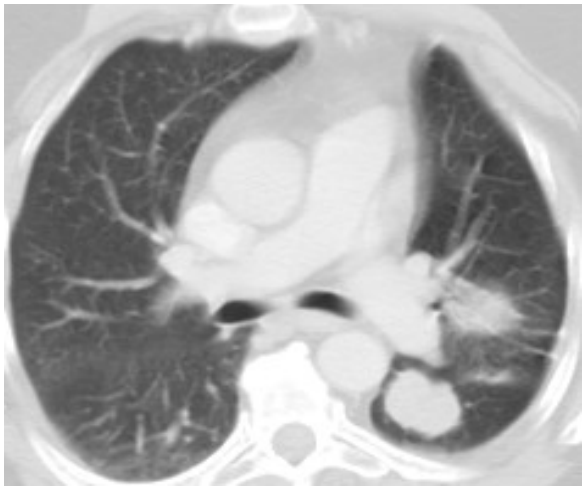


Figure 1: Initial CT at the level of the left hilum showed large left hilar mass 3.9x3.5x4.9cm in her left lung. Left lower lobe mass was 2.4cmx2.9cm and multiple nodules were seen on the left. A lytic lesion was seen in the humeral head.

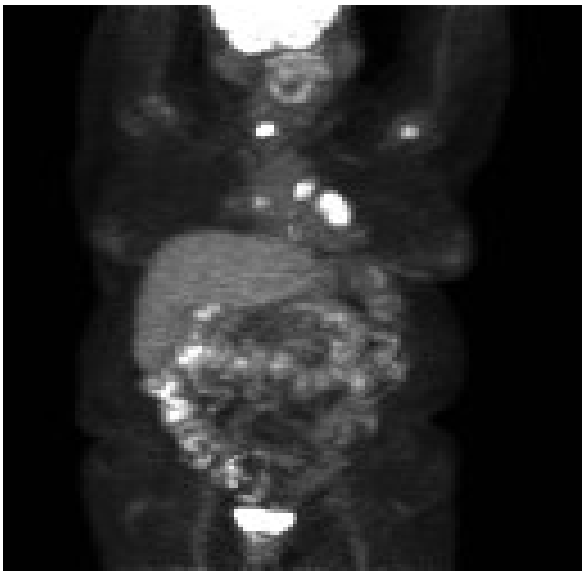


Figure 2: Pet CT showed multiple hypermetabolic masses at the left lung, the largest at the left lower lobe perihilar region with SUV 15.8; hilar mass; metabolic activity within the right thyroid nodule; destructive metastatic lesion in the left humeral head.

© 2016 Global Journals Inc. (US)

Figure 3: Two weeks following the beginning Erlotinib treatment (4 weeks following radiation therapy), she reported a dry cough and dyspnea on exertion. Her pulse ox dropped to 92% after ambulation. A CT scan showed smaller masses and scarring in the left lower lobe in the area of surgery. The majority of the pleural-based nodules that were present on prior examination were no longer seen.

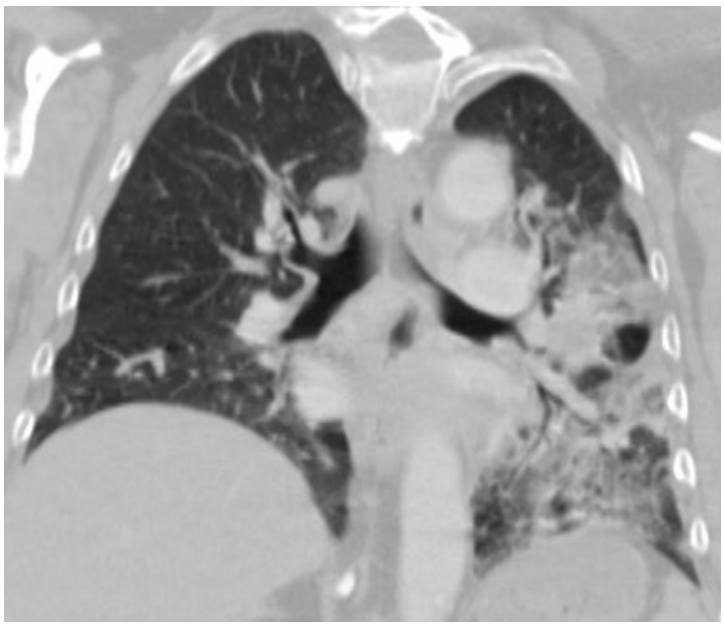


Figure 4: Approximately one month later, she reported increased SOB without hemoptysis, fevers, or chills. Repeat CT scan showed smaller masses, but new left lung infiltrates and an area of consolidation in the left lung that vaguely outlined the radiation port. There was an associated left pleural effusion.

© 2016 Global Journals Inc. (US)

Figure 5: Repeat axial enhanced CT chest revealed bilateral diffuse pneumomediastinum with posterior displacement of the heart, and worsening airspaces, sparing the apices. The patient was severely dyspneic as evident by respiratory motion. Blood gas: pH 7.38, pc02 56, and o2 sat of 86%. Her disease progressed and the patient expired under comfort measures.

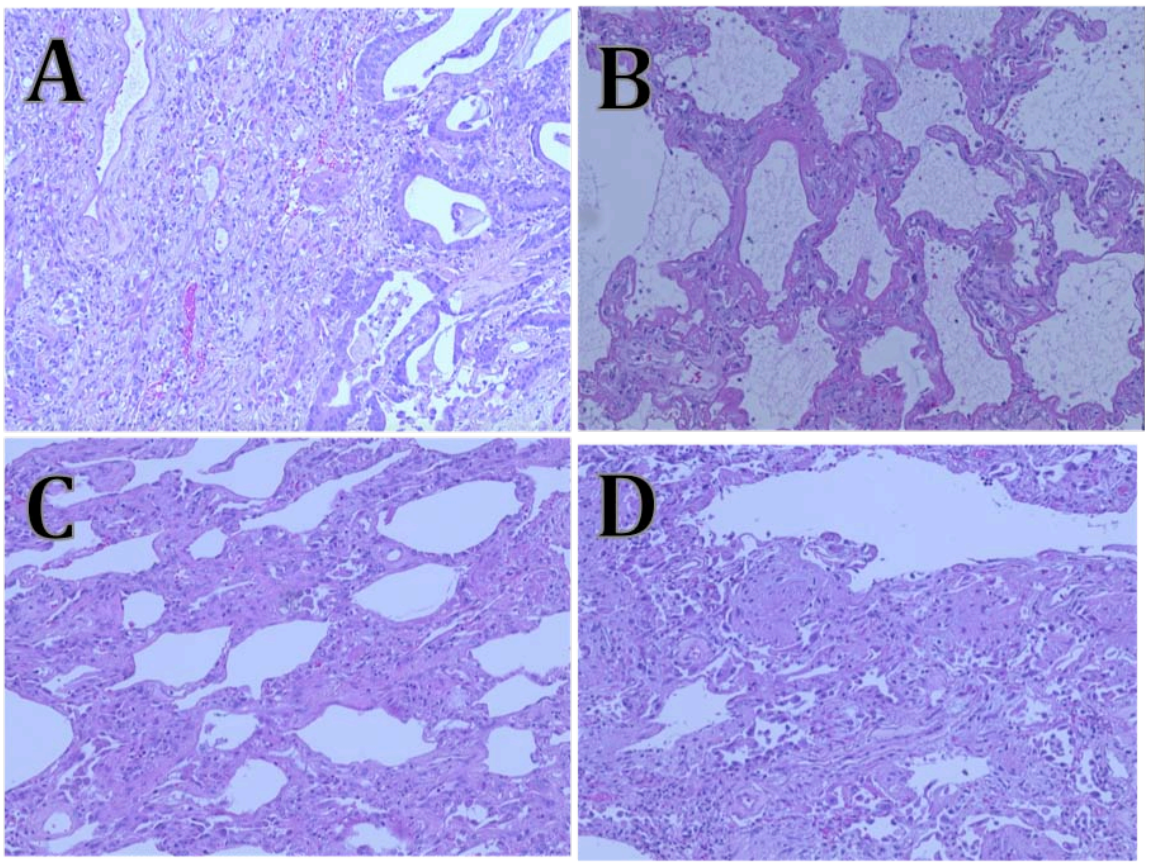


Figure 6: A/B: LUL and LLL: The left upper and lower lobes with end-stage diffuse alveolar damage: marked squamous metaplasia and fibroblastic proliferation, bronchiolar dilatation, marked fibrosis and honeycombing of the interstitium.

C: RUL with early diffuse alveolar damage: marked edema in the airspaces, mild interstitial fibrosis, and alveoli lined with hyaline membranes

D: RLL with acute, organizing proliferative diffuse alveolar damage: increased Type II pneumocytes, increased interstitial fibrosis, and squamous metaplasia.

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

The Effect of Green Leafy Vegetable Intake on the Incidence of Urothelial Cancers: A Meta- Analysis

By Dr. Richard Lee Pollock
Lamar State College Port Arthur, United States

Abstract- Study objective was to hypothesized that the consumption of green leafy vegetables (GLV), including cruciferous vegetables (CV), significantly reduces the incidence of urothelial cancers. The hypothesis was answered by using the experimental approach of meta-analysis by synthesizing relevant worldwide studies that address the association between the consumption of GLV and risk of incidence of the disease. Three models were used, and the first indicated an overall odds ratio effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on urothelial cancer as: OR = 0.749 (95% CI .678 to .827), p<.001. The second model indicated an overall hazard ratio effect size as: HR = 0.803 (95% CI .699 to .922), p=.002. The third model indicated an overall risk ratio effect size as: RR = 0.896 (95% CI .691 to 1.16), p=.405.

Keywords: green leafy vegetables; cruciferous vegetables; random effect model; effect size; forest plot; meta-analysis.

GJMR-F Classification: NLMC Code: WJ140

Strictly as per the compliance and regulations of:

© 2016. Dr. Richard Lee Pollock. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/ 3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

The Effect of Green Leafy Vegetable Intake on the Incidence of Urothelial Cancers: A Meta-Analysis

Dr. Richard Lee Pollock

Abstract- Study objective was to hypothesized that the consumption of green leafy vegetables (GLV), including cruciferous vegetables (CV), significantly reduces the incidence of urothelial cancers. The hypothesis was answered by using the experimental approach of meta-analysis by synthesizing relevant worldwide studies that address the association between the consumption of GLV and risk of incidence of the disease. Three models were used, and the first indicated an overall odds ratio effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on urothelial cancer as: *OR* = 0.749 (95% *CI* .678 to .827), $p<.001$. The second model indicated an overall hazard ratio effect size as: *HR* = 0.803 (95% *CI* .699 to .922), $p=.002$. The third model indicated an overall risk ratio effect size as: *RR* = 0.896 (95% *CI* .691 to 1.16), $p=.405$.

Keywords: green leafy vegetables; cruciferous vegetables; random effect model; effect size; forest plot; meta-analysis.

I. Introduction

Histologically, urothelial cancer strikes the urinary bladder, ureter, and renal pelvis (kidney). Urothelial cancer generally originates in the mucosa of the lower urinary tract. Urothelial cancer is the 7th most common worldwide cancer among men, accounting for about 200,000 new annual cases (Zeegers, Goldbohm, & van den Brandt, [1]). Over the past four decades, Zeegers et al. write many epidemiological studies suggest that urothelial cancers are influenced by environmental factors, including tobacco smoking, fluid intake, exposures to industrial chemicals, and diet. Smoking is certainly an established risk factor for urothelial cancer, and high intake of vegetables or fruits are believed to reduce the risk of urothelial cancer (Sakauchi et al., [2]).

This study will contribute to people's understanding of the importance of a daily intake of green leafy vegetables (GLV), including cruciferous vegetables (CV). GLV come from a wide variety of plants all over the world, and nearly one thousand species of plants with edible leaves are known. GLV most often come from short-lived herbaceous plants such as lettuce and spinach. CV are mostly green leafy vegetables from the family *Cruciferae* that are widely cultivated, with many genera, species, and cultivars being raised for food production. Examples are cauliflower, cabbage, cress, bok choy, broccoli, kale, collard greens and similar green leafy vegetables and their roots. Studies indicate long-term intake of GLV and the micronutrients they contain may reduce risk of Type 2 diabetes, CVD and some types of cancers (Carter, Gray, Troughton, Khunti, & Davies, [3]; Joshipura et al., [4]; Smith-Warner et al., [5]). Limited knowledge about the importance of GLV consumption appears to be a serious worldwide health problem. This meta-analysis study further emphasized the importance of this association by synthesizing multiple source studies researched worldwide on the topic of GLV intake and incidence of urothelial cancers.

The research hypothesis of this study is the consumption of green leafy vegetables (GLV) including cruciferous vegetables (CV) will significantly reduce the incidence of urothelial cancers. There is a need to research peer-reviewed journals to investigate case-control studies, prospective cohort studies, and comparative studies dealing with GLV intake and the incidence of these horrific diseases. This meta-analysis was used to investigate the effects of daily GLV, including CV, intake on the incidence of these type cancers, not just in the United States but worldwide, and to show if this relationship is a significant one. This meta-analysis research approach filled a knowledge gap by combining data from multiple studies to a common effect size and statistically examining relations between study characteristics and findings. Findings between these different studies were compared by transforming the results into a single common effect size to better understand the apparent contradictions in prior research findings.

II. Methods and Materials

Searching for relevant studies was primarily performed by computer search engines. PubMed Central, Academic Search Complete, Medline, Proquest Central, Science Direct, Google, and Yahoo online were the most frequently used online periodical databases. The criteria for including studies in the meta-analysis included: (1) those occurring between 1980 to 2015; (2) those appearing full-text in scholarly journals; (3) those

Author: Ph.D, Assistant Professor Lamar State College Port Arthur, Texas, 1500 Proctor Street, Port Arthur, USA.
e-mail: pollockrl@lamarpa.edu

© 2016 Global Journals Inc. (US)

showing no severe methodological flaws; (4) the collection of primary studies had to be a collaborative cohort, case-control, population-based cohort, or a prospective cohort study design; (5) those including relations between similar independent variables (GLV intake levels including CV) and dependent variables (incidence of urothelial cancer); (6) all studies had to measure GLV consumption, which was estimated by highest versus lowest quantiles (quintiles, or quartiles, or tertiles); (7) those that reported an effect size of: odds ratio (OR), or risk ratio (RR), or hazard ratio (HR), and their respective 95% confidence intervals (CI) data; and (8) source studies collected in this meta-analysis had to use logistic regression or Cox regression models to control for confounding or interaction variables and the results were expressed as adjusted effect size ratios if needed.

All meta-analysis calculations were performed by the software package Comprehensive Meta-Analysis Version 2 by Biostat(CMA v.2). CMA v.2 was developed specifically for use in meta-analysis. These calculations include determining effect sizes (HR, OR, RR, and their 95% CI), heterogeneity of the studies, relative weights for each study, significance (p) for each study, and for determining methods for detecting the presence of publication bias and assessing its impact on the meta-analysis. CMA v.2 was also used to create a high-resolution plot (Forest plot) that shows all the combined studies, their p-value, common effect size, 95% CI for each study, relative weights for each study, and either a fixed effect model or random effect model.Separate meta-analyses were calculated for each effect size, because OR, RR, or HR, cannot be converted into each other.

The relative weights for each study were calculated by the CMA v.2 software package. Small studies tend to have wide confidence intervals and large studies tend to have narrow confidence intervals with larger studies given greater percent relative weights (Higgins, Hedges, Borenstein, & Rothstein, [6]). An effect size of 1.00 represents no treatment effect. Whereas when the effect size falls below 1.00, this indicates participants who consumed GLV in the highest quartile were less likely to develop urothelial cancer. If the effect size falls above 1.00, this indicates study subjects were more likely to develop the disease due to GLV intake in the highest intake quartile. The 95% CI bounding in each study reflects the precision of the estimate, with small studies tending to have wide 95% CI and large studies tending to have narrow 95% CI (Higgins et al., [6]). The use of 95% CI in this meta-analysis was used, so each meta-analysis performed in this study was statistically significant ($p < .05$) if and only if the confidence interval excluded the null value of 1.0 for each effect model synthesized (Higgins et al., [6]). The conventional value of significance level for this meta-analysis was pre-set to an alpha of 0.05 (Stigler, [7]).

CMA v.2 allows the meta-analyst to record data by subgroups within the study. Some studies collected in this meta-analysis used subgroups, e.g., male, female, GLV, and CV. In this study, it emerged that the effect sizes were comparable for each subgroup, so it was decided to use the study as the unit of analysis. This required calculating a "combined" effect size (utilizing the CMA v.2 software) for subgroups within each study, and imputes the values for the full group, which recorded one treatment effect for each study. CMA v.2 was also used to detect the possible presence of publication bias. All studies used in this meta-analysis were examined using a funnel plot of the natural logarithm of the effect size versus its precision (1/standard error). Begg and Mazumdar's test for correlation, Egger's test for regression, Duval and Tweedie's trim and fill, and the classic fail-safe method were also calculated by CMA v.2 software for detecting the presence of publication bias and assessing its impact on this meta-analysis study.

III. Results

Over a two-year search period (2012-2015), thousands of scientific papers were reviewed for this meta-analysis. Table 1 shows the total number of collected studies (N=13) that were relevant and reviewed in this meta-analysis. Four studies were combined in meta-analysis that examined the relationship between GLV intake and the incidence of urothelial cancer and used HR as the effect size. Three studies were combined that included the relationship between GLV intake and incidence of urothelial cancer and used RR as the effect size. Six case-control studies were combined that included the relations between GLV intake and the incidence urothelial cancer and used OR as the effect size.

a) Research Question

Does an increased intake of GLV significantly reduce incidence of urothelial cancer?

b) Urothelial Cancer ----- OR

Six studies met the inclusion criteria that investigated the relationship between the incidences of urothelial cancer with the intake of GLV. The six studies shown had a similar common effect size (OR), and a meta-analysis was used to combine results from the six different studies. Figure 1 shows a Forest plot of the six studies and meta-analysis. The random effect model was selected for combining the source studies. The random effect model indicates an overall OR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on urothelial cancer as: $OR = 0.749$ (95% CI .678 to .827), $p < .001$. Note: In the Grieb et al. [8] study, Hsu et al. [9] study, and the Wakai et al. [10] study, OR results for subgroups GLV and CV were combined to calculate one treatment effect for each source study. Also, the Hu et al. [11] study combined

© 2016 Global Journals Inc. (US)

male, female, GLV, and CV results to calculate one treatment effect for each source study. Brock et al. [12], and Zhao et al. [13] did not combine variables in their studies.

c) Detecting the Presence of Publication Bias--- OR

All the collected studies were evaluated for the likelihood of publication bias using a funnel plot of the log odds ratio versus its precision (1/standard error), Begg and Mazumdar's test for correlation, Egger's test for regression, Duval and Tweedie's trim and fill, and Classic fail-safe method. Note in Supplementary Figure 1 that the large urothelial cancer studies appear toward the top of the funnel plot graph, and tend to cluster near the mean of the log OR in the relationship between six urothelial cancer studies. The smaller studies appear toward the bottom of the funnel plot, and since there is more random variation in smaller studies, they are dispersed across a wide range of log OR. Supplementary Figure 1 shows a possible presence of publication bias in the six studies with the studies distributed asymmetrically about the mean effect size. By contrast, in the absence of publication bias, the bottom of the funnel plot would tend to show an even concentration of studies around the mean (Borenstein et al., [14]). Duval and Tweedie's method imputes two missing studies to the right and adjusts new *OR*= 0.757, 95% *CI* = 0.688 to 0.834 from the observed values (0.749, 95% *CI* = 0.678 to 0.827). Begg and Mazumdar's rank correlation *p*-value (2-tailed) = .35, indicating no evidence of publication bias. Egger's linear regression *p*-value (2-tailed) = .38, also indicating no evidence of publication bias. Classic fail-safe N test imputes there would be 41 missing studies that would bring the *p*-value to >.05.

d) Urothelial Cancer ---------- HR

Four studies met the inclusion criteria that investigated the relationship between the incidences of urothelial cancer with the intake of GLV. The four studies shown had a similar common effect size (HR) and a meta-analysis was used to combine results from the four different studies. Figure 2 shows a Forest plot of the four studies and meta-analysis. The random effect model was selected for combining the source studies. This model indicates an overall HR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on incidence of urothelial cancer as: *HR* = 0.803 (95% *CI* .699 to .922), *p*=.002. Note: In the Park et al. [15] study, HR results for subgroups GLV, CV, male, and female were combined to calculate one treatment effect for each source study. Sakauchi et al. [16], Ros et al. [17], and Tang et al. [18] did not combine variables in their studies.

e) Detecting the Presence of Publication Bias------ HR

Supplementary Figure 2 shows no evidence of publication bias in the four studies, with the studies distributed symmetrically about the mean effect size. Duval and Tweedie's method imputes missing studies to the right and adjusts new *HR* = 0.805, 95% *CI* = 0.703 to 0.922 from the observed values (0.803, 95% *CI* = 0.699 to 0.922). Begg and Mazumdar's rank correlation *p*-value (2-tailed) = 1.00, indicating no evidence of publication bias. Egger's linear regression *p*-value (2-tailed) = .679, also indicating no evidence of publication bias. Classic fail-safe N test imputes there would be 4 missing studies that would bring the *p*-value to >.05.

f) Urothelial Cancer ---------- RR

Three studies met the inclusion criteria that investigated the relationship between the incidences of urothelial cancer with the intake of GLV. The three studies shown had a similar common effect size (RR), and a meta-analysis was used to combine results from the three different studies. Figure 3 shows a Forest plot of the studies and meta-analysis. The random effect model was selected for combining the source studies. This indicates an overall RR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on incidence of urothelial cancer as: *RR* = 0.896 (95% *CI* .691 to 1.16), *p*=.405. Note: In the Zeegers et al. [19] study, RR results for subgroups cooked GLV and raw GLV were combined to calculate one treatment effect for each source study. In the Michaud et al. [20] study, GLV and CV were combined to calculate one treatment effect for this source study. Michaud et al. [21] did not combine variables in their study.

g) Detecting the Presence of Publication Bias------ RR

Supplemental Figure 3 shows no evidence of publication bias in the three studies, with the studies distributed symmetrically about the mean effect size. Duval and Tweedie's method imputes zero missing studies to the right and calculates no adjusts of *RR* = 0.896, 95% *CI* = 0.691 to 1.160 from the observed values (0.896, 95% *CI* = 0.691 to 1.160). Begg and Mazumdar's rank correlation *p*-value (2-tailed) = 0.602, indicating no evidence of publication bias. Egger's linear regression *p*-value (2-tailed) = 0.967, also indicating no evidence of publication bias. Classic fail-safe N test imputes there would be 0 missing studies that would bring the *p*-value to >.05.

IV. Discussion of Findings

The intent of this study was to investigate potential influences of GLV intake on incidences of urothelial cancer worldwide. An extensive search for relevant studies was initiated to learn more about these diet-disease relationships. Only 13 studies were collected and used in three separate meta-analysis. However, this meta-analysis study included 979,363 total participants collected from the 13 source studies. The research questions in this meta-analysis study was; does an increased intake of GLV significantly reduce the

© 2016 Global Journals Inc. (US)

worldwide incidence of urothelial cancers studied? Even after adjusting effect sizes for possible publication bias via Duval and Tweedie's method, all three meta-analysis results indicated GLV consumption reduced urothelial cancer incidences, and two of the three meta-analysis results were significant. Six case-control studies were collected that investigated the relationship between the incidences of urothelial cancers with the consumption of GLV and used OR as their effect size. These studies included 14,194 case participants and controls, with 3,823 case participants having urothelial cancers. The random effect model indicated an overall OR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on cancer as: *OR* = 0.749 (95% *CI* .678 to .827), $p<.001$, showing 25.1% lower odds that an intake of GLV significantly reduces the incidence of urothelial cancers in the highest intake category as compared with the lowest. Just four prospective cohort studies were collected that investigated the relationship between the incidences of urothelial cancers with the consumption of GLV and used HR as their effect size. However, these four studies included 769,297 participants with 1,855 diagnosed with urothelial cancers. The random effect model indicated an overall HR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on cancer as: *HR* = 0.803 (95% *CI* .699 to .922), $p=.002$, which indicated an increased intake of GLV significantly reduces the incidences of urothelial cancers by 19.7%. Just three worldwide prospective cohort studies were collected that investigated the relationship between the incidences of urothelial cancers with the consumption of GLV and used RR as their effect size. However, these three studies included 195,872 participants with 1,134 cases with urothelial cancer. The random effect model indicated an overall RR effect size of the 'almost every day' highest vs. lowest quantile intake category of GLV on cancer as: *RR* = 0.896 (95% *CI* .691 to 1.160), $p=.405$. The RR results indicate that increased GLV intake non-significantly reduces the incidence of these urothelial cancers by 10.4%.

a) Phytochemicals in GLV Reduce Incidence of Diseases

Cancer is a group of more than 100 different types of malignancies, and there are several potential substances in GLV that my exhibit anticancer effects (Rajalakshmi & Agalyaa, [22]). GLV are typically high in dietary fiber, iron, calcium, and very high in phytochemicals and nutrients such as vitamin C, carotenoids, lutein, folate, magnesium as well as vitamin K. The primary dietary source of vitamin K is generally GLV and both in vitro in vivo studies have shown that vitamin K exhibits anticancer effects (Chlebowski, Akaman, & Block, [23]). Vitamin K has also been shown to inhibit the growth of mammalian tumor cells in culture (Prasad, Edwards-Prasad, & Sakamoto, [24]). Also, GLV are high in carotenoids such as beta-carotene, and in animal experiments they were shown to suppress liver carcinogenesis (Moreno et al., [25]). Carotenoids found in GLV have antioxidant potential in the scavenging of harmful free radicals (Krinsky, [26]) and they appear to play an important role in the prevention of hepatitis virus-related liver carcinogensis (Kurahashi et al., [27]). Also, due to the potent anti-proliferative effects of isothiocyanates on bladder cancer in in vitro and in vivo experiments, CV consumption may play a role in survival among patients with bladder cancer (Tang et al., [18]). In the 2010 decade, researchers are conducting extensive research studies to discover phytochemicals connections to disease prevention, but so far, solid evidence is mostly lacking (DeBruyne, Pinna, & Whitney, [28]). There are thousands of these phytochemicals in GLV and researchers are just beginning to understand and theorize how a handful of these phytochemicals work to reduce incidence of cancer and other diseases, and what is current in the 2010 decade may change tomorrow (DeBruyne, Pinna, & Whitney, [28]).

V. Acknowledgements

IRB at Trident University International ethically approved the content of this meta-analysis (no human subjects used). No conflict of interests are declared with this research, and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Theory and editing were improved in this paper by my dissertation committee which included Dr Mickey Shachar, Dr Frank Gomez, and Dr Kyung-Ae Son-Guidry.

References Références Referencias

1. Zeegers MP, Goldbohm RA., van den Brandt PA. Consumption of vegetables and fruits and urothelial cancer incidence: A prospective study. *American Association for Cancer Research* 2001; 10: 1121-1128.
2. Sakauchi F, Mori M, Mashio M, Watanabe Y, Ozasa K, Hayashi K, et al. Dietary habits and risk of urothelial cancer death in a large-scale cohort study (JACC study) in Japan. *Nutr Cancer* 2004; 50: 33–39.
3. Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: Systematic review and meta-analysis. *BMJ (Clinical Research Ed.)* 2010; 341: c4229.
4. Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA: The Journal of the American Medical Association* 1999; 282: 1233-9.
5. Smith-Warner SA, Spiegelman D,Yaun SS, Adami HO, Beeson WL, van Den Brandt P, et al. Intake of

© 2016 Global Journals Inc. (US)

fruits and vegetables and risk of breast cancer: A pooled analysis of cohort studies. *The Journal of the American Medical Association* 2001; 285: 769-76.
6. Higgins JP, Hedges LV, Borenstein M, Rothstein HR. *Introduction to meta-analysis.* New York: John Wiley & Sons; 2009.
7. Stigler S. Fisher and the 5% level. *Chance;* 200821: 12.
8. Grieb SM, Theis RP, Burr D, Benardot D, Siddiqui T, Asal NR. Food groups and renal cell carcinoma: Results from a case-control study. *J Am Diet Assoc* 2009; 109: 656-667.
9. Hsu CC, Chow W, Boffetta P, Moore L, Zaridze D, Moukeria A, et al. Dietary risk factors for kidney cancer in eastern and central Europe. *Am J Epidemiol* 2007; 166: 62-63.
10. Wakai K, Hirose K, Takezaki T, Hamajima N, Ogura Y, Nakamura S, et al. Foods and beverages in relation to urothelial cancer: Case-control study in Japan. *IntUrogynecol J* 2004; 11:11-19.
11. Hu J, Mao Y, White K. Diet and vitamin or mineral supplements and risk of renal cell carcinoma in Canada. *Cancer Causes & Control* 2003; 14: 705-714.
12. Brock KE, Ke L, Gridley G, Chiu BC, Ershow AG, Lynch CF. Fruit, vegetables, fibre and micronutrients and risk of US renal cell carcinoma. *Br J Nutr* 2012; 108: 1077-1085.
13. Zhao H, Lin J, Grossman HB, Hernandez LM, Dinney CP, Wu X. Dietary isothiocyanates, GSTM1, GSTT1, NAT2 polymorphisms and bladder cancer risk. *Int J Cancer* 2007; 120: 2208-2213.
14. Borenstein M, Hedges LV, Higgins, JP, Rothstein HR. *Introduction to meta-analysis (statistics in practice).* 1st ed. Hoboken, NJ: Wiley Publication; 2009.
15. Park S, Ollberding NJ, Woolcott CG, Wilkens LR, Henderson BE, Kolonel LN. Fruit and vegetable intakes are associated with lower risk of bladder cancer among women in the Multiethnic Cohort Study. *J Nutr* 2013; 143: 1283-1292. DOI:10.3945/jn.113.174920
16. Sakauchi F, Mori M, Mashio M, Watanabe Y, Ozasa K, Hayashi K, et al. Dietary habits and risk of urothelial cancer death in a large-scale cohort study (JACC study) in Japan. *NutrCancer* 2004 50: 33–39.
17. Ros MM, Bueno-de-Mesquita HB, Kampman E, Buchner FL, Aben KK, Egevad L, et al. Fruit and vegetable consumption and risk of aggressive and non-aggressive urothelial cell carcinomas in the European prospective investigation into cancer and nutrition. *Eur J Cancer* 2012; 48: 3267-3277.
18. Tang L, Zirpoli GR, Guru K, Moysich KB, Zhang Y, Ambrosone CB, McMann SE. Intake of cruciferous vegetables modifies bladder cancer survival. *Cancer Epidemiol Biomarkers Prev*. 2010; 19: 1806-1811.
19. Zeegers MP, Goldbohm RA, van den Brandt PA. Consumption of vegetables and fruits and urothelial cancer incidence: A prospective study. *American Association for Cancer Research* 2001; 10: 1121-1128.
20. Michaud DS, Spiegelman D, Clinton SK, Rimm EB. Fruit and vegetable intake and incidence of bladder cancer in a male prospective cohort. *J Natl Cancer Inst*1999; 91: 605-613.
21. Michaud DS, Pietinen P, Taylor PR, Virtanen M, Virtamo M, Albanes D. Intakes of fruits and vegetables, carotenoids and vitamins A, E, C in relation to the risk of bladder cancer in the ATBC cohort study. *Br J Cancer* 2002; 87: 960-965.
22. Rajalakshmi, PA, Agalyaa S. Docking analysis of phenethyl isothiocyanates from nasturtium officinale (watercress), on 4 – (methylnitrosamino) -1- (3 – pyridyl) – 1 – butanone (NNK), carcinogenic action in oral cancer. *Int J Pharma Bio Sci* 2010; 1: 67-74.
23. Chlebowski RT, Akaman SA, Block, JB. Vitamin K in the treatment of cancer. *Cancer Treat Rev*1985; 12:49-63.
24. Prasad KN, Edwards-Prasad, J, Sakamoto A. Vitamin K3 (menadione) inhibits the growth of mammalian tumor cells in culture. *J LifeSci* 1981; 29: 1387-1392.
25. Morena FS, S-Wu T, Naves MM, Silveira ER, Oloris SC, da Costa MA, et al. Inhibitory effects of beta-carotene and vitamin a during the progression phase of hepatocarcinogensis involve inhibition of cell proliferation but not alteration in DNA methylation. *Nutr Cancer* 2002; 44: 80-88.
26. Krinsky NI. Carotenoids as chemopreventive agents. *Prev Med* 1989; 18: 592-602.
27. Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: A prospective cohort study in Japan. *Br J Cancer* 2009; 100: 181-184.
28. DeBruyne LK, Pinna K, Whitney E. *Nutrition & diet therapy*. 7th ed. California: Thomson and Wadsworth; 2011.

© 2016 Global Journals Inc. (US)

Table 1: Location of the studies, number (N) of participants per study (N = cases + controls), and effect size used per study.

Study N		Location	Effect Size
Hsu et al. (2007)	2,574	Europe	OR
Hu et al. (2003)	6,649	Canada	OR
Brock et al. (2012)	2,150	USA	OR
Grieb et al. (2009)	672	USA	OR
Wakai et al. (2004)	744	Japan	OR
Zhao et al. (2007)	1,405	USA	OR
Sakauchi et al. (2004)	114,517	Japan	HR
Ros et al. (2012)	468,656	Europe	HR
Tang et al. (2010)	239	United States	HR
Park et al. (2013)	185,885	United States	HR
Zeegers et al. (2001)	120,852	Netherlands	RR
Michaud et al. (1999)	47,909	United States	RR
Michaud et al. (2002)	27,111	Finland	RR

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Brock et al. (2012)	CV	0.800	0.527	1.215	0.296	5.62
Grieb et al. (2009)	Combined	0.573	0.297	1.104	0.096	2.28
Hsu et al. (2007)	Combined	0.837	0.709	0.990	0.037	35.19
Hu et al. (2003)	Combined	0.703	0.593	0.834	0.000	33.79
Wakai et al. (2004)	Combined	0.649	0.377	1.116	0.118	3.34
Zhao et al. (2007)	CV	0.710	0.568	0.887	0.003	19.78
Radom effect model		**0.749**	**0.678**	**0.827**	**0.000**	

Statistics for each study — Odds ratio and 95% CI

0.1 0.2 0.5 1 2 5 10

Figure 1: Forest plot showing a significant 25.1% lower risk of incidence from urothelial cancer by consuming a high quantile intake of GLV.

Study name	Subgroup within study	Hazard ratio	Lower limit	Upper limit	p-Value	Relative weight
Park et al. (2013)	Combined	0.798	0.664	0.958	0.016	57.37
Ros et al. (2012)	GLV	0.800	0.621	1.031	0.085	29.88
Sakauchi et al. (2004)	GLV	0.760	0.419	1.378	0.366	5.44
Tang et al. (2010)	CV	0.890	0.533	1.487	0.656	7.30
Random effect model		**0.803**	**0.699**	**0.922**	**0.002**	

Statistics for each study — Hazard ratio and 95% CI

0.10.2 0.5 1 2 5 10

Figure 2: Forest plot showing a significant 19.7% lower risk of incidence from urothelial cancer by consuming a high quantile intake of GLV.

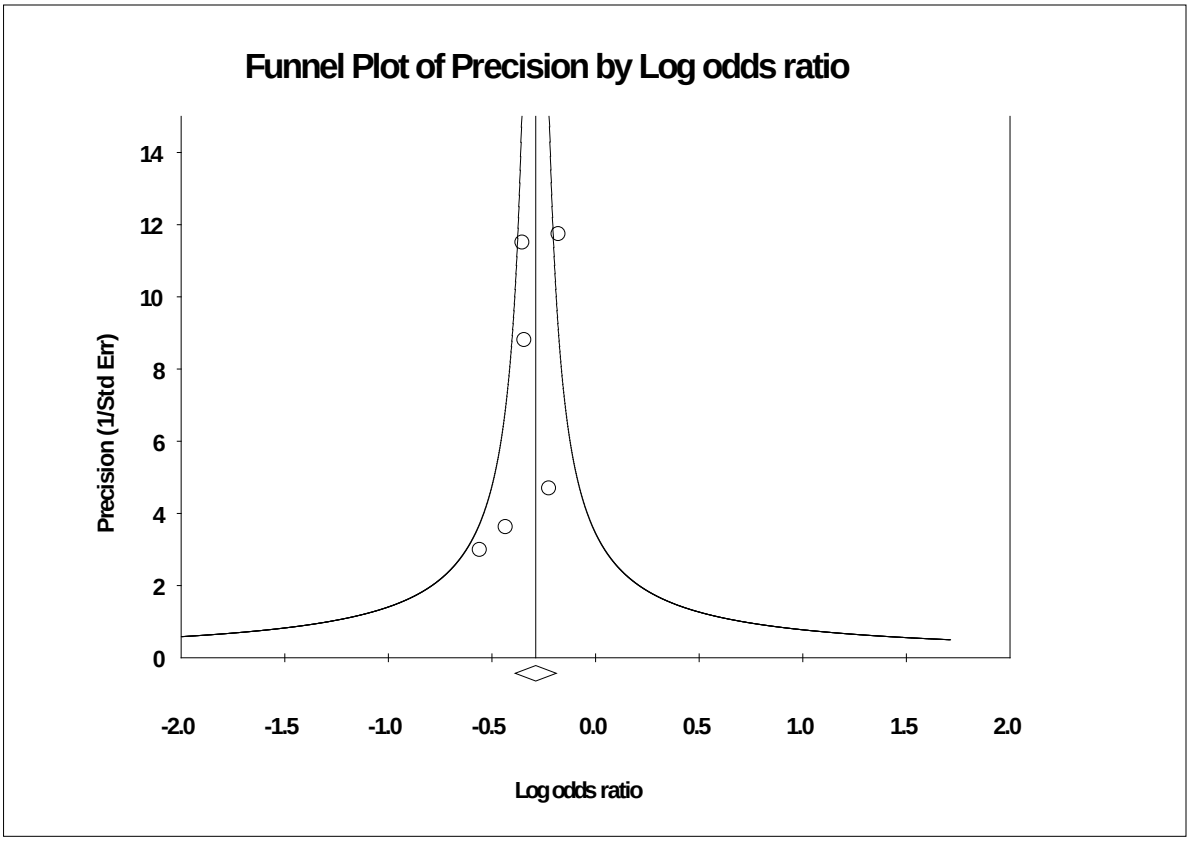
Study name	Subgroup within study	Risk ratio	Lower limit	Upper limit	p-Value	Relative weight
Zeegers et al. (2001)	Combined	0.920	0.753	1.124	0.414	40.76
Michaud et al. (1999)	Combined	0.681	0.500	0.929	0.015	30.36
Michaud et al. (2002)	CV Men	1.150	0.828	1.597	0.404	28.88
Random effect model		**0. 896**	**0.691**	**1.160**	**0.405**	

Statistics for each study — Risk ratio and 95% CI

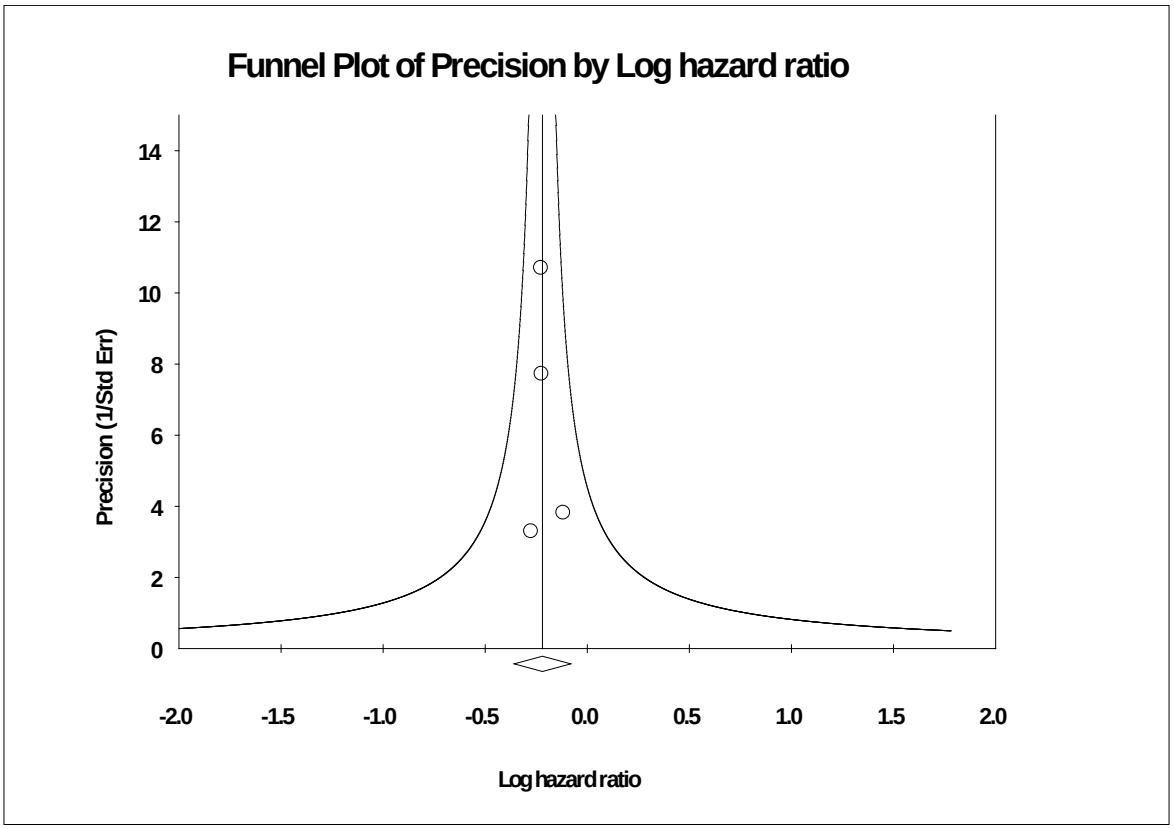
0.1 0.2 0.5 1 2 5 10

Figure 3: Forest plot showing non-significant 10.4% lower risk of incidence from urothelial cancer by consuming the highest quantile intake of GLV compared to the lowest quantile intake.

© 2016 Global Journals Inc. (US)

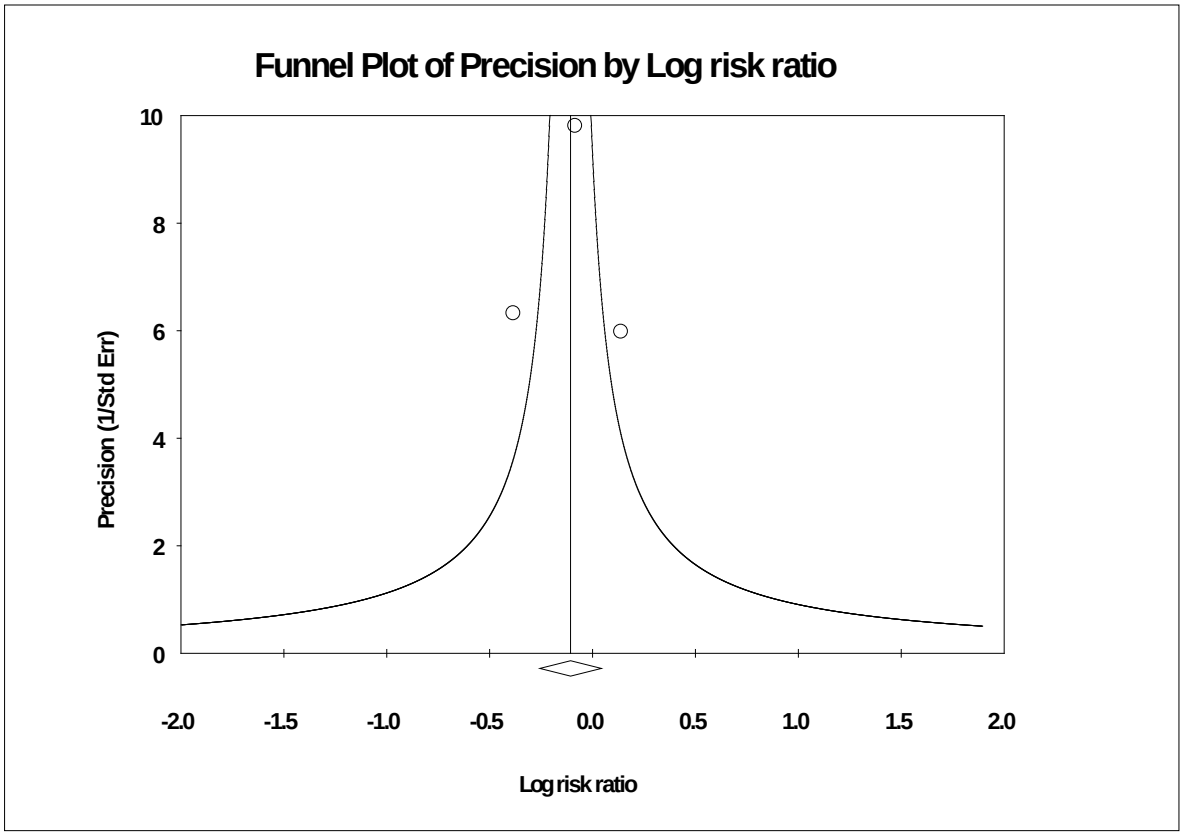


Supplementary Figure 1: Funnel plot showing six studies with four studies on the left of mean log odds ratio and two on the right signifying possible presence of publication bias.



Supplementary Figure 2: Funnel plot showing four studies with one study on the left of mean log hazard ratio and one on the right signifying possible absence of publication bias.

© 2016 Global Journals Inc. (US)



Supplementary Figure 3: Funnel plot showing three studies with one study on the left of mean log risk ratio and one on the right signifying possible absence of publication bias.

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Waldenstrom's Macroglobulinema Presenting as Syncope

By Ramy Sedhom, Daniel Sedhom, Angela Samaan & Syed Haqqie
Rutgers Robert Wood Johnson Medical School, United States

Abstract- Syncope is a common complaint usually secondary to neurologic, cardiovascular, or orthostatic causes. However, rare etiologies are possible, implicating a great importance to history, physical examination, and interpretation of laboratory results and diagnostic workup. Waldenstrom's Macro-globulinema (WM) is a B-cell Lymphoma, hallmarked by an over-production of IgM. Neurologic manifestations of WM include visual or auditory disturbances, headache, confusion, dizziness, vertigo, stroke and rarely, syncope. Neurologic presentations are a result of hyperviscosity or direct infiltration of malignant cells into the CNS. We present a case of Waldenstrom's Macroglublinema associated syncope.

GJMR-F Classification: NLMC Code: WB182

Strictly as per the compliance and regulations of:

© 2016. Ramy Sedhom, Daniel Sedhom, Angela Samaan & Syed Haqqie. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Waldenstrom's Macroglobulinema Presenting as Syncope

Ramy Sedhom [α], Daniel Sedhom [σ], Angela Samaan [ρ] & Syed Haqqie [ω]

Abstract- Syncope is a common complaint usually secondary to neurologic, cardiovascular, or orthostatic causes. However, rare etiologies are possible, implicating a great importance to history, physical examination, and interpretation of laboratory results and diagnostic workup. Waldenstrom's Macroglobulinema (WM) is a B-cell Lymphoma, hallmarked by an overproduction of IgM. Neurologic manifestations of WM include visual or auditory disturbances, headache, confusion, dizziness, vertigo, stroke and rarely, syncope. Neurologic presentations are a result of hyperviscosity or direct infiltration of malignant cells into the CNS. We present a case of Waldenstrom's Macroglublinema associated syncope.

I. Introduction

Syncope is a common presenting problem evaluated by clinicians in internal medicine. Syncope associated hospitalizations have a high cost on our health care system. Neurally mediated syncope is implicated in the majority of cases, followed by cardiovascular disease and orthostatic hypotension. The work-up for syncope is often not helpful. The importance of a good history cannot be overstated, as it often leads the clinician to the most probable diagnosis. Waldenstrom's Macroglobulinemia is a lymphoplasmacytic malignancy that secretes IgM. Patients with WM may have neurologic manifestations either from hyperviscosity or related to direct infiltration of lymphoplasmacytic cells into the CSF. This is well described as the Bing Neel syndrome. Neurologic manifestations include visual and auditory disturbances, headache, confusion, dizziness, vertigo, and rarely syncope or stroke.

II. Case Report

A 71-year-old man presented with syncope. For 3 months, he was evaluated several times by his primary care provider, and in urgent care facilities, for episodes of both syncope and pre-syncope. Review of symptoms was positive for fatigue, nausea, visual floaters, and hearing loss. He reported several falls in the past six months. He reported that symptoms prior to his falls were sudden, without a preceding prodrome. He felt unsteady with positional changes. He denied vertigo or dizziness. He was prescribed meclizine, by several providers, without any benefit.

Author α σ ω: Department of Internal Medicine, Albany Medical College, Albany, New York. e-mail: sedhomr@gmail.com
Author ρ: Department of Internal Medicine, New York Institute of Technology College of Osteopathic Medicine, Old Westbury, New York.

On the day of admission, he reported a near syncopal event while watching a football game. He sustained no injuries from his fall. His grandson, who witnessed it, denied any jerking or twitching movements. The patient's grandson denied any confusion and the patient was lucid immediately following the event. During his prior episodes, he was not urinating, defecating, or straining. He denied palpitations, diaphoresis, or chest pain. He reported a 40-pound weight loss in the six months preceding this current hospitalization. Several months prior, he suffered a lower gastrointestinal bleed. He was not on any blood thinners and denied taking ibuprofein or over the counter medications. A colonoscopy during that hospitalization demonstrated internal hemorrhoids. He had no evidence of malignancy on either upper or lower endoscopy. Past medical history included diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, and iron deficiency anemia. His home medications included lisinopril, metformin, iron tablets, atorvastatin, and meclizine. He lived with his wife and was completely independent for all activities of daily living. She was his only sexual partner. He smokes cigarettes but denies alcohol use. He has no history of cardiac disease, heart failure, or arrhythmia.

On physical exam, his vital signs were heart rate of 84 bpm, blood pressure of 147/81 mmHg, respiratory rate of 16, and temperature of 98.5 °F. Orthostatic vital signs were normal. Cardiac exam revealed regular rate and rhythm without murmurs or gallops. Abdominal, pulmonary, vascular, skin, and lymph node examination was normal. His neurological exam revealed normal strength, and intact cranial nerves, without sensory deficits. His gait was within normal limits. Romberg testing was normal. Lab data was notable for a hematocrit 25.6 %, hemoglobin 8.0 g/dL, MCV 93.6 fL, BUN 30 mg/dL, creatinine 1.6 mg/dL, glucose 256 mg/dL, calcium of 9.3 mg/dL, total protein of 9.7 mg/dL, albumin of 2.4 mg/dL, and a mild lactic acid of 4.6 mg/dL. Urinalysis was positive for evidence of proteinuria. The remainder of laboratory testing was within normal limits. EKG revealed sinus tachycardia without any acute ST changes or history suggestive of prior coronary disease.

Magnetic resonance imaging of the brain and neck did not show any significant stenosis. Carotid Doppler was normal and transthoracic echocardiogram did not reveal any wall motion abnormalities, a normal

© 2016 Global Journals Inc. (US)

ejection fraction, and evidence of only mild (grade I) diastolic dysfunction.

III. Discussion of Differential Diagnosis

Orthostasic hypotension as a result from his anemia and prior gastrointestinal bleeding was considered initially as a potential diagnosis. However, further history and review of prior records revealed that prior episodes of syncope preceded the admission for gastrointestinal bleeding. In addition, his admissions for reported gastrointestinal bleeding never required blood transfusions and his hemoglobin levels were always stable. Cardiac examination and imaging narrowed the differential diagnosis, as there was no indication of aortic stenosis or a clinically significant outflow obstruction. Neurologic examination was only helpful in ruling out diagnosis, but was otherwise not helpful in leading to a more probable cause. The weight loss was of great interest to the medical team. It was not typical to elicit or consider in the acute presentation of syncope. It assisted in making an alternative diagnosis.

Looking closer at some of his laboratory results, we inquired for a unifying diagnosis that can further explain his renal insufficiency, proteinuria, anemia, elevated lactic acid, and protein-albumin gap. Though he had presented to multiple institutions with an elevation of his baseline creatinine, it was never worked up at any of the outside institutions. Telemetry testing was performed numerous times and was always normal. Orthostatic hypotension was ruled out during initial vital signs and also was never positive at any of his prior visits. We decided to investigate his elevated protein/albumin gap, which was found in the setting of anemia and kidney injury, in an elderly male. A major concern and an important diagnosis to consider was multiple myeloma.

His completed work-up included serum protein electrophoresis (SPEP), serum immunofixation and free light chain testing. SPEP demonstrated the presence of an IgM kappa monoclonal band, with an elevated IgM level at 8090 mg/dL.

The patient's underwent bone marrow biopsy and results were consistent with lymphoplasmacytic lymphoma. Serum viscosity was elevated at 9.2 centipoises. Following review of his clinical story, bone marrow biopsy, and cytogenetics, a diagnosis of Waldenström's macroglobulinemia was made. The patient first tolerated plasmapheresis followed by chemotherapy. At 6-month follow-up, his symptoms had resolved, and he had no further episodes of syncope.

IV. Conclusions

Syncope work-up should be highlighted by a detailed history and physical exam, and not driven by imaging or diagnostic testing. In our patient, renal insufficiency, proteinuria, anemia, elevated lactic acid level, and protein/albumin gap, suggested an atypical cause of syncope. Waldenström's macroglobulinemia is associated with elevated IgM levels. IgM, a pentamer, if elevated, can cause symptoms related to hyperviscosity. In our patient, it explained his neurologic symptoms. Common neurologic syndromes in the literature include vertigo, hearing loss, changes in vision, and ataxia. Headache, altered mental status, stroke and seizures, have also been described. Rarely, hyperviscosity can cause syncope. Hyperviscosity is a clinical diagnosis, and treatment should be started prior to the return of test results. This case highlights the importance of clinical thinking in the workup of syncope.

Works Cited

1. Lin P, Medeiros L. Lymphoplasmacytic Lymphoma/ Waldenstrom Macroglobulinemia. Advances in Anatomic Pathology. 2005; 12(5): 246-255.
2. Ansell S, Kyle R, Reeder C, Fonseca R, Mikhael J, Morice W et al. Diagnosis and Management of Waldenström Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines. Mayo Clinic Proceedings. 2010; 85(9): 824-833.
3. Ritzenthaler T, Leray V, Bourdin G, Baudry T, Domnisoru I, Ghesquières H et al. Ventriculitis revealing Bing-Neel syndrome in a patient without Waldenstrom's macroglobulinemia. Clinical Neurology and Neurosurgery. 2013; 115(1): 82-84.
4. Sanchez-Guerrero SCastillo J. Bing-Neel syndrome: a rare complication of Waldenstrom macroglobulinemia. Blood. 2015; 126(11): 1390-1390.
5. Stone MBogen S. Evidence-based focused review of management of hyperviscosity syndrome. Blood. 2011; 119(10): 2205-2208.

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Central Neurogenic Hyperventilation with Acute Respiratory Alkalosis, Transient Lactic Acidosis and Tachycardia Following Endoscopic Third Ventriculostomy in a Child- A Case Report

By Fajish Habib, Tejas Mehta, Ahamed Lafir Aliyar, Ahmed Sayed Youssef, Adnan Khan & Neeraj Kumar

Abstract- Background: Central neurogenic hyperventilation (CNH) is a rare but well documented complication after endoscopic third ventriculostomy (ETV) in adults.

Case Characteristics: 6 year old developed CNH, acute respiratory alkalosis, intraoperative tachycardia and lactic acidosis following ETV for a pineal gland tumour causing obstructive hydrocephalus.

Observations: Attributed to irritation of the hypothalamus while irrigating the floor of the thrid ventricle with normal saline.

Outcome: Treatment with sedation and oxygen via rebreathing mask resulted in normalization of symptoms and blood gas.

Keywords: third ventriculostomy, respiratory alkalosis, central neurogenic hyperventilation, saline irrigation.

GJMR-F Classification: NLMC Code: WL 141.5.N4

Strictly as per the compliance and regulations of:

© 2016. Fajish Habib, Tejas Mehta, Ahamed Lafir Aliyar, Ahmed Sayed Youssef, Adnan Khan & Neeraj Kumar. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Central Neurogenic Hyperventilation with Acute Respiratory Alkalosis, Transient Lactic Acidosis and Tachycardia Following Endoscopic Third Ventriculostomy in a Child- A Case Report

Fajish Habib [α], Tejas Mehta [σ], Ahamed Lafir Aliyar [ρ], Ahmed Sayed Youssef [ω], Adnan Khan [¥] & Neeraj Kumar [§]

Abstract- ***Background:*** Central neurogenic hyperventilation (CNH) is a rare but well documented complication after endoscopic third ventriculostomy (ETV) in adults.

Case Characteristics: 6 year old developed CNH, acute respiratory alkalosis, intraoperative tachycardia and lactic acidosis following ETV for a pineal gland tumour causing obstructive hydrocephalus.

Observations: Attributed to irritation of the hypothalamus while irrigating the floor of the thrid ventricle with normal saline.

Outcome: Treatment with sedation and oxygen via rebreathing mask resulted in normalization of symptoms and blood gas.

Message: CNH can occur in children following ETV and should be recognized early. Measurement of ICP during ETV and use of alternative irrigation fluids such as lactated ringer's or artificial CSF may minimize occurrence.

Keywords: third ventriculostomy, respiratory alkalosis, central neurogenic hyperventilation, saline irrigation.

I. Introduction

Endoscopic third ventriculostomy is a common, minimal-invasive neurosurgical procedure, performed most frequently for patients with obstructive hydrocephalus secondary to impediment of cerebrospinal fluid (CSF) flow across the Aqueduct of Sylvius or the outlets of the fourth ventricle. [1,2]The procedure involves creating a fenestration on the floor of the third ventricle to create a communication between the third ventricle and the basal cisterns as a bypass route for the CSF flow. [3]Complications of ETV include varying degrees of intraventricular hemorrhage, CSF leak, pneumocephalus, arrhythmias (tachycardia and bradycardia) and injury to periventricular structures.[3,4] We present the first pediatric case with intraoperative tachycardia as a result of normal saline irrigation during ETV followed by central neurogenic hyperventilation (CNH) with acute respiratory alkalosis and transient lactic acidosis.

Author α σ ρ ω ¥ §: Departments of Pediatric Intensive Care, Neuro-surgery and Anesthesiology, Hamad Medical Corporation, Doha, Qatar. e-mail: fajish@hotmail.com

II. Case Report

a) History and physical examination

A 6-year old, previously healthy girl was admitted to the pediatric ward in Hamad General Hospital with ataxic gait, visual disturbances, difficulty in writing, urinary and fecal incontinence for three months. There was no history of seizures, headache, vomiting or altered sensorium. The child was conscious, alert with intact higher mental functions. Her weight was 25 kg (90th centile), height was 113 cm (50th centile). Heart rate upon presentation was 110 bpm, blood pressure was 100/60 mmHg and respiratory rate was 30 per minute. Examination was significant for Parinaud's syndrome with upward gaze palsy, weakness of the right side with hyperreflexia and positive Babinski's sign on the right side. Fundoscopy revealed Grade 4 papilledema bilaterally but pupils were symmetrical and reactive bilaterally. Urgent MRI of the head (figure 1) revealed a large, irregular, lobular tumor mass in the posterior part of third ventricle and pineal region with involvement of the thalamus and mid brain. There was consequential rapid onset obstructive hydrocephalus. Differential diagnosis included parapinealglioma, pineoblastoma and germinoma. Her serum electrolytes revealed hyponatremia (134mmol/L), which was corrected using normal saline infusion. Other laboratory tests including a complete blood count, coagulation profile, liver and renal functions were within normal limits.

The patient was seen by the neurosurgical team and the decision was taken to perform an endoscopic third ventriculostomy, with an external ventricular drainage catheter insertion followed by biopsy from the tumour mass.

b) Intraoperative course

The patient was intubated, sedated and BP was monitored invasively. Anesthesia was maintained with target -controlled infusion of propofol at 4-5mcg/ml amounting to a total cumulative dose of ~5mg/kg/hr. Intraoperative end-tidal CO_2 was maintained between 32-38mmHg. During the surgical procedure, the

© 2016 Global Journals Inc. (US)

operative field was being continuously irrigated with normal saline at room temperature. Neuroendoscopic intracranial pressure was not being monitored due to lack of required equipment. From the onset of surgery the patient developed gradual increase in HR from a baseline of 90-100 beats/min to 110-120 beats/min, 1mcg/kg fentanyl was given as a bolus to rule out pain as the cause of tachycardia with no subsequent reductions in heart rate. The intraoperative blood gas (Table1) at this stage revealed pH 7.40, $PaCO_2$ 33mmHg, HCO_3^- 20 mmol/L, base excess -3.7 mmol/L.

The tumor from the right side was biopsied and specimens were obtained for histopathological diagnosis. Septostomy was performed using bipolar and bleeding was encountered from the edges. After the septostomy, normal saline at room temperature was used to irrigate the ventricles under high pressure using a 50cc syringe to minimise the hemostasis, which resulted in a marked increase in the heart rate to 150-160 beats/min. Blood pressure during the time rose to 140-130/70-80. The surgeons were informed, and the scopes were immediately withdrawn and drainage of CSF was done, which drained visibly under very high pressure. Following the sudden drainage of CSF, the heart rate dropped down to 130-140 and the ETCO2 dipped transiently to 24 from 32 mmHg. Arterial blood gas at this stage revealed a pH 7.31, $PaCO_2$ 39.1 mmHg, HCO_3^- 19.9mmol/L, base excess -7 mmol/L. The patient received yet another bolus of fentanyl 1mcg/kg for the possibility of pain induced tachycardia, but there was no response. The total duration of surgery was 4 hours 30 minutes and the patient was successfully extubated at the operating theatre after ensuring adequate voluntary respiration and was then transferred to the PICU for further observation.

c) Postoperative Course

The patient continued to have tachycardia with HR ranging 140-150/min. Her BP was 120/70 mmHg and the patient was tachypneoic with RR reaching 50 /min. ABG done 1 hour after the procedure revealed fully compensated respiratory alkalosis with metabolic acidosis pH 7.43, PaCO2 13.0 mmHg, HCO_3^- 9.1mmol/L, base excess -13.6 mmol/L, glucose 14.9 mmol/L and lactate 4.3 mmol/L. Although the patient was fully conscious, alert and euvolemic, a bolus of normal saline was administered to see if there would be any change in HR or RR and there was none. The patient was still hyperventilating with tachycardia and an ABG repeated 2 hours from surgery showed no change in the respiratory alkalosis and metabolic acidosis with pH 7.38 $PaCO_2$ 13.2 mmHg, HCO_3^- 8.0mmol/L, base excess -13.1 mmol/L, lactic acid 4.9 mmol/L. As the cause for the hyperventilation and lactic acidosis was unclear a dose of 1mEq/kg of 8.4% sodium bicarbonate was administered as symptomatic treatment. The HR dropped to 120-130 per minute and RR to 35-40 per minute. Follow-up ABG, 6 hours from the procedure showed an uncompensated respiratory alkalosis with pH 7.51, $PaCO_2$ 16.6mmHg, HCO_3^- 13.5 mmol/L, base excess -8 mmol/L and lactic acid 1.4 mmol/L. The child was more irritable and had started to complain of fear and nightmares. She also developed fever with a core temperature of 38.5^0C. A suspicion of central neurogenic hyperventilation was raised at this stage and the patient was put on oxygen via a rebreathing facemask. The patient was sedated with lorazepam of 0.1mg/kg intravenously. ABG after 8 hours from the procedure showed an improvement in the respiratory alkalosis with pH 7.46, $PaCO_2$ 26.6 mmHg, HCO_3^- 21.1 mmol/L, base excess -4 mmol/L and lactic acid 1.0 mmol/L. HR dropped to 110-120 per minute and RR to 25-30 per minute, almost 12 hours after the surgery. 16 hours from surgery her ABG was back to normal with pH 7.42, $PaCO_2$ 32.2 mmHg, HCO_3^- 22.0 mmol/L, base excess-2.7 mmol/L, lactic acid 0.4 mmol/L. The patient was transferred to the pediatric ward on the second post-operative day. The biopsy revealed a final diagnosis of WHO grade 1 Pilocytic Astrocytoma.

III. Discussion

Hyperventilation can be central or peripheral. However, when it does occur, peripheral causes have to be ruled out first. There are numerous causes for peripheral hyperventilation such as fever, pain, asthma, pneumothorax, pulmonary embolism, drugs, alcohol withdrawal, ischemic heart disease and congestive heart failure, hyperthyroidism.[5] Reported first by Plum and Swanson in 1959, central neurogenic hyperventilation (CNH) is a rare respiratory syndromedefined as an abnormally regular, rapid (>25 to 30 breaths/min) breathing pattern that cannot be explained by hypoxemia.[6]CNH can either be persistent or transient. Persistent CNH is seen most commonly due to tumors, especially with pontine involvement.[7] Of the various mechanisms that have been described, CNH has been thought to occur mainly due to the disconnection between pontine and medullary respiratory centers leading to unopposed stimulation of the latter or from acidosis due to lactate production by tumor mass, thereby activating the brainstem chemosensitive respiratory neurons.[7]

Our case is an example of transient CNH, which is one of the rare but documented complications following endoscopic third ventriculostomy. [4,8-10]As reported previously, the proposed mechanism of CNH following ETV is due to a transient hypothalamic dysfunction caused by unrecognized rise in intra-cranial pressure while irrigating the third ventricle with normal saline under high pressure.[8,11,12] The floor of the third ventricle is formed by a part of the hypothalamus and it is this hypothalamic dysfunction, which was responsible for the tachycardia, hypertension and

© 2016 Global Journals Inc. (US)

hyperthermia that was seen in our patient as a part of the midbrain dysregulation syndrome reported previously by Pranzatelli et al.[12] The initial management of CNH is with delivery of oxygen via a rebreather mask and use of benzodiazepines to sedate the patient. In severe cases, where patients can have irritability and altered sensorium, mechanical ventilation maybe required to control the hyperventilation.[8,9]

Although uncommon, it is pertinent that the anesthesiologists, neurosurgeons and critical care teams involved be aware of such significant intra and post-operative hemodynamic disturbances which can occur following an ETV. Such a dramatic clinical presentation, as in our case, can pose quite a difficult diagnostic challenge to pinpoint the exact etiology unless it is specifically looked for. Again, this case, along with those reported previously, highlights the necessity of intraoperative intracranial pressure monitoring during neurosurgical interventions.[8,9]

The transient lactic acidosis associated with the CNH and acute respiratory alkalosis is a novel feature of our case, as none of the previously reported cases in literature have suggested a transient serum lactic acidosis as secondary sequelae of the CNH, which in turn can occur as a complication of ETV. We were unable to attribute a cause for the elevated serum lactate initially; however, there have been detailed studies, which looked into the association of hyperventilation with lactic acidosis and found that there is a strong correlation.[13-15]Hyperventilation has been shown to increase the basal concentration and reduce the elimination of lactic acid, thereby inducing lactic acidosis throughout the period of hyperventilation.[13] This happened to be the case in our patient who had elevated serum lactate as long as she was hyperventilating, following which the levels returned to normal. We recommend measurement of lactic acid levels in all patients with CNH to gain more insight, as there have been no previous reports of an association between CNH and lactic acidosis per se.

The type of neurosurgical fluid used for irrigation during neurosurgical procedures has been the subject of debate for a long time. The detrimental effects of normal saline on neural tissue especially in neuroendoscopic surgeries, due to the large volume of saline used for irrigation in a closed space, has been highlighted in a review by Syed et al.[16] They have suggested, based on previous physiological studies, that normal saline has a much different composition to CSF, which is the natural irrigant. Composition of normal saline is different form CSF in terms of pH, osmolality and presence of bicarbonate-which is the key buffer in normal CSF. The continuous loss of carbon dioxide normally from neural cells, combined with the absence of the buffering action offered by bicarbonate and slightly acidic pH (6.4) of normal saline may lead to brain damage. Moreover, the lack of K^+, Ca^{2+}, and Mg^{2+} in normal saline may contribute to its unfavorable effects on neural tissue.[16-19] Artificial CSF followed by lactated ringer's solution share the most similarities in terms of physiological resemblance (pH, osmolality and inorganic ions content) to CSF and are the fluids of choice for various authors for brain irrigation during neuroendoscopic procedures.[16-21] The hyperventilation associated with our case could be partly associated with CSF acidosis induced by normal saline used for brain irrigation during the ETV.[1] Hence, more detailed studies are needed to look into usage of artificial CSF and lactated ringer's as substitutes for normal saline as the irrigating fluids of choice, especially for neuroendoscopic procedures.

In conclusion, ETV may cause intra-operative hemodynamic disturbances such as tachycardia, hypertension and hyperthermia followed by post-operative transient hypothalamic dysfunction and CSF acidosis leading to sequelae of central neurogenic hyperventilation with acute respiratory alkalosis and transient lactic acidosis. We would like to emphasize the importance of ICP monitoring during neuroendoscopic procedures, as an in advertant rise in ICP appears to be the central factor leading to the various ill effects encountered both intra and post operatively. Moreover, normal saline has been the irrigation fluid of choice for neurosurgeons, although a multitude of laboratory studies suggest normal saline being less than ideal for the purpose. It might be prudent to look into alternatives, namely artificial CSF and ringer's lactate.

Disclosure

The authors report no conflict of interest concerning the findings specified in this paper.

References Références Referencias

1. Huhn SL, Feaster WW, Larson CP. Pediatric surgery. In: Anesthesiologist's Manual of Surgical Procedures. 3rd ed. Edited by Jaffe RA, Samuels SI: Philadelphia, Lippincott Williams & Willikins. 2004, pp 945-8.
2. El-Dawlatly A, Elgamal E, Murshid W, Alwatidy S, Jamjoom Z, Alshaer A. Anesthesia for third ventriculostomy. A report of 128 cases. Middle East J Anesthesiol 2008; 19: 847-57.
3. Ganjoo P, Sethi S, Tandon M S, Chawla R, Singh D. Incidence and pattern of intraoperative hemodynamic response to endoscopic third ventriculostomy. Neurol India 2009; 57: 162-5.
4. Walker ML: Complications of third ventriculostomy. Neurosurg Clin N Am 15: 61-66, 2004.
5. Mason RJ, Broaddus VC, Martin TR, King TE Jr, Schraufnagel DE, Murray JF, et al.: Murray & Nadel's textbook of respiratory medicine, ed 5: Saunders Elsevier, 2010, pg1842-1847.
6. Plum F, Swanson AG. Central neurogenic hyperventilation in man. Arch Neurol Psychiat 1959; 81: 535-49.

© 2016 Global Journals Inc. (US)

7. Tarulli AW, Lim C, Bui JD, Saper CB, Alexander MP. Central Neurogenic Hyperventilation: A Case Report and Discussion of Pathophysiology. *Arch Neurol.* 2005; 62(10): 1632-1634.
8. Sung HJ, Sohn JT, Kim JG, Shin IW, Ok SH, Lee HK, et al.: Acute respiratory alkalosis occurring after endoscopic third ventriculostomy - a case report. Korean J Anesthesiol 59: S194-S196, 2010.
9. Hae Mi Lee, M.D., Kyung Bae Shin, M.D., Seong Ho Kim, M.D., Dae Lim Jee, M.D.; An Acute Postoperative Intractable Hyperventilation after an Endoscopic Third Ventriculostomy. J Korean Neurosurg Soc 51: 173-176, 2012.
10. Souto-Ferro JM, Valero-Castell R, F. bregas-Juli. N, Carrero Cardenal E. Postoperative respiratory alkalosis as a complication of neuroendoscopy. Rev Esp Anestesiol Reanim 1997; 44: 83-5.
11. Fabregas N, L.pez A, Valero R, Carrero E, Caral L, Ferrer E. Anesthetic management of surgical neuroendoscopies: usefulness of monitor pressure inside the neuroendoscope. J Neurosurg Anesthesiol 2000; 12: 21-8.
12. Pranzatelli MR, Pavlakis SG, Gould RJ, De Vivo DC. Hypothalamicmidbrain dysregulation syndrome: hypertension, hyperthermia, hyperventilation, and decerebration. J Child Neurol 1991; 6: 115-22.
13. Druml W, Grimm G, Laggner AN, Lenz K, Schneeweiss B; Lactic acid kinetics in respiratory alkalosis. Crit Care Med. 1991 Sep; 19(9): 1120-4.
14. Yoshiyasu Ueda, Masayo Aizawa, Atsushi Takahashi, Masamitsu Fujii and Yoshitaka Isaka; Exaggerated compensatory response to acute respiratory alkalosis in panic disorder is induced by increased lactic acid production. Nephrol Dial Transplant (2009) 24: 825–828.
15. Chiba T., Ishii H., Takahashi S., Yano T.; Relationship between blood lactate and hyperventilation during high-intensity constant-load exercise in heat. Biol. Sport 2011;28:159-163.
16. Syed Faraz Kazim, Syed Ather Enam, Muhammad ShahzadShamim. Possible detrimental effects of neurosurgical irrigation fluids on neural tissue: An evidence based analysis of various irrigants used in contemporary neurosurgical practice. International Journal of Surgery 8 (2010) 586-590.
17. Uchida K, Yamada M, Hayashi T, Mine Y, Kawase T. Possible harmful effects on central nervous system cells in the use of physiological saline as an irrigant during neurosurgical procedures. Surg Neurol 2004; 62: 96-105.
18. Fujita Y, Doi K, Harada D, Kamikawa S. Modulation of physiological hemostasis by irrigation solution: comparison of various irrigation solutions using a mouse brain surface bleeding model. J Neurosurg 2010; 112: 824-8.
19. Nishimura M, Doi K, Naito S. Pharmacological assessment of ARTCEREB irrigation and perfusion solution for cerebrospinal surgery using primary cultures of rat brain cells. J Toxicol Sci. 2010 Aug; 35(4): 447-57.
20. Doi K, Kawano T, Morioka Y, Fujita Y, Nishimura M. Various irrigation fluids affect postoperative brain edema and cellular damage during experimental neurosurgery in rats. Surg Neurol 2006; 66:565-71.
21. Oka K, Yamamoto M, Nonaka T, Tomonaga M. The significance of artificial cerebrospinal fluid as perfusate and endoneurosurgery. Neurosurgery 1996; 38: 733-6.

© 2016 Global Journals Inc. (US)

Figure Legend

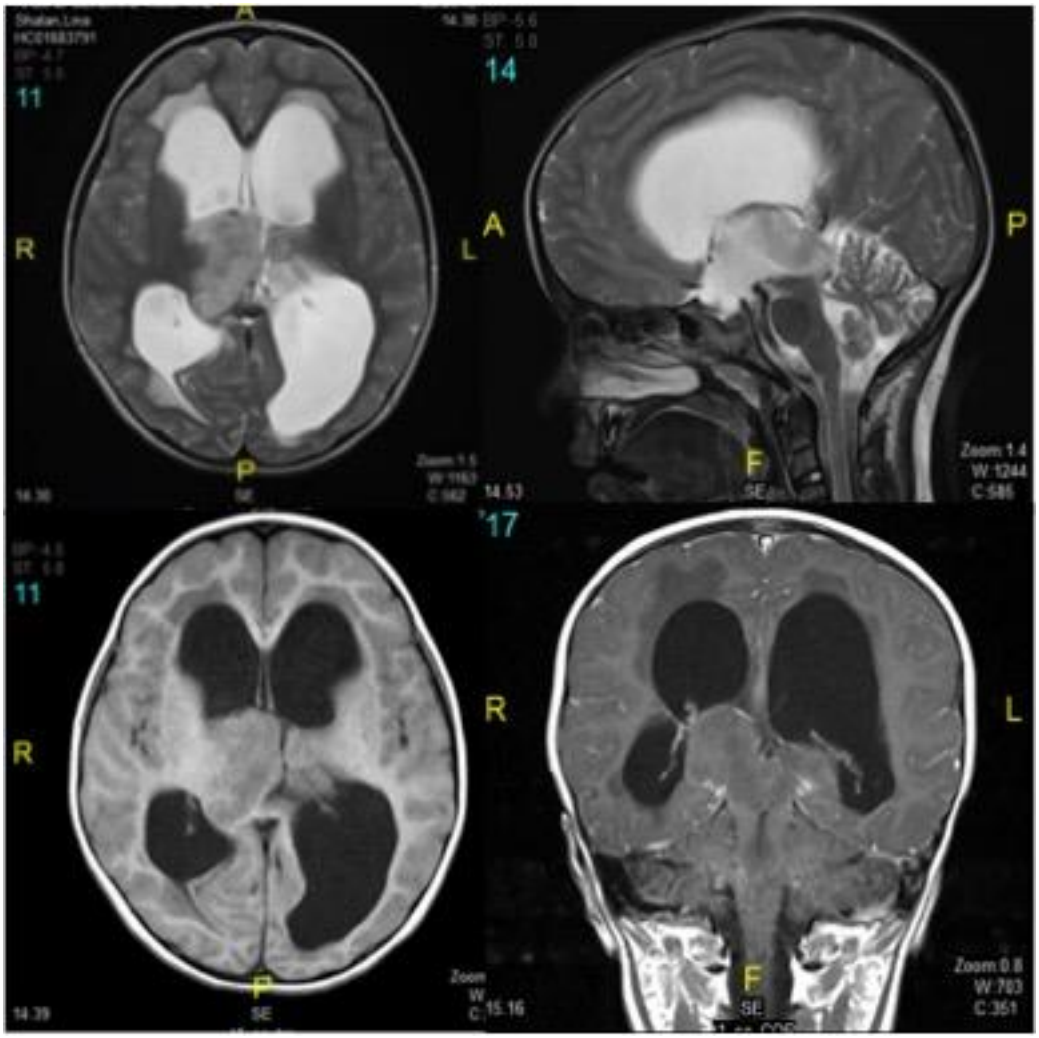


Figure 1: Preoperative MRI showing a large, irregular, lobular tumor mass in the posterior part of third ventricle and pineal region with involvement of the thalamus and mid brain

Table 1: Arterial blood gas analysis

	pH	$PaCO_2$ (mmHg)	HCO_3^- (mmol/L)	B.E (mmol/L)	Lactate (mmol/L)
90 min into surgery	7.40	32.9	20.6	-3.7	0.4
4 hours into surgery	7.31	39.1	19.9	-7.0	1.5
1 hour post-surgery	7.43	13.0	9.1	-13.6	4.3
2 hours post-surgery	7.38	13.6	8.1	-15.4	4.9
6 hours post surgery	7.51	16.6	13.5	-8.4	1.4
8 hours post surgery	7.46	26.6	21.1	-4.0	1.0
16 hours post surgery	7.42	32.6	22	-2.7	0.4

© 2016 Global Journals Inc. (US)

This page is intentionally left blank

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Describe the Various Types of Neuropathy Observed in Patients with Diabetes

By Ismat Abedlrhman Alborhan Mohammed
Cardiff University, United Kingdom

Introduction- The most widely recognized neuropathic syndrome found in individuals with diabetes is diabetic peripheral neuropathy. Diabetes is the commonest reason for neuropathy around the world, creating an extensive range of disorders including diverse forms of nerves and pathological mechanisms such as ischemic, metabolic, compressive and immunologic.[12] There are different forms of diabetic neuropathies (diffuse or focal) which present with various clinical sign and influencing distinctive parts of the nervous system. The common forms of neuropathies are autonomic neuropathies and chronic sensorimotor distal symmetric polyneuropathy (DPN). Diagnosis of DPN is reached by excluding other disorder that exhibits the same signs.[3] Approximately, 8% of general population suffer from long standing pain are caused by the neuropathic pain.[4] Around 50% of chronic diabetics' individuals (more than 25 years) will develop neuropathy which affect their daily living.[5] Hyperglycaemia is the chief reason of advancement of all neuropathies, counting PDN. The Diabetes Control and Complications Trial (DCCT) demonstrated that good glycaemic control will lessen the occurrence of neuropathy up to 60%.[6]

GJMR-F Classification: NLMC Code: WQ 248

Strictly as per the compliance and regulations of:

© 2016. Ismat Abedlrhman Alborhan Mohammed. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Describe the Various Types of Neuropathy Observed in Patients with Diabetes

Ismat Abedlrhman Alborhan Mohammed

I. Introduction

The most widely recognized neuropathic syndrome found in individuals with diabetes is diabetic peripheral neuropathy. Diabetes is the commonest reason for neuropathy around the world, creating an extensive range of disorders including diverse forms of nerves and pathological mechanisms such as ischemic, metabolic, compressive and immunologic.[12] There are different forms of diabetic neuropathies (diffuse or focal) which present with various clinical sign and influencing distinctive parts of the nervous system. The common forms of neuropathies are autonomic neuropathies and chronic sensorimotor distal symmetric polyneuropathy (DPN). Diagnosis of DPN is reached by excluding other disorder that exhibits the same signs.[3] Approximately, 8% of general population suffer from long standing pain are caused by the neuropathic pain.[4] Around 50% of chronic diabetics' individuals (more than 25 years) will develop neuropathy which affect their daily living.[5] Hyperglycaemia is the chief reason of advancement of all neuropathies, counting PDN. The Diabetes Control and Complications Trial (DCCT) demonstrated that good glycaemic control will lessen the occurrence of neuropathy up to 60%.[6]

II. Signs and Symptoms of Neuropathy

The pain accompanying with PDN is often refer to as numbness, tingling pain, or augmented due to touch. It may also be labelled as electrical, burning, or stabbing with paraesthesia, deep aching and hyperesthesia. The pain is classically more at night-time. PDN characteristically progresses in the lower legs and feet. Allodynia (excruciating sensations to mild stimuli) and hyperalgesia (augmented sensitivity to painful sensations) may also develop.[78]

Warning sign of nerve impairment may comprise:[9]

- Tingling and numbness, or pain in the toes, arms, legs feet and hands
- hands and feet muscle wasting
- Nausea, or vomiting
- Constipation or diarrhoea
- Faintness or dizziness due to postural hypotension
- Urinary problems
- Erectile dysfunction in men or vaginal dryness in women
- weakness

Approximately, 20% of all diabetic persons and about a third of individuals with DPN are suffer from painful symptoms like tingling, burning (paraesthesia or 'pins and needles'), shooting or stabbing.[1011]

III. Diabetic Peripheral Neuropathy Pathophysiology

The diabetic peripheral neuropathy pathophysiology still not fully understood. A few studies have shown that the ideal way to avert or deferral diabetic peripheral neuropathy is a close control of glycaemia.[12] Numerous theories of pathogenesis have been distinguished in the aetiology of DN such as: [13]

- Oxidative-nitrosative stress
- Neuroinflammation
- Mitochondrial dysfunction
- Bioenergetic crisis
- Axon-glia interactions
- Demyelination

Some recent studies have demonstrated that nearly 30% of diabetic patients are influenced by distal symmetric polyneuropathy. In T1DM patient, the EURODIAB prospective complications study found a prevalence rate of 28% for distal symmetrical polyneuropathy.[14]

Theories concerning the numerous aetiologies of diabetic neuropathy comprise:[15]

- Nerve fibers injury by metabolic disorder.
- Insufficiency of nerve and blood vessels
- Impaired autoimmune
- Deficient of neurohormonal growth factor

Nevertheless, Current studies have demonstrated that both metabolic interactions and vascular factors are included at all steps of DPN.[16]Neuropathic pain mechanisms can be summarized in following table:[17]

Author: Cardiff University. e-mail: asmatme@hotmail.com

© 2016 Global Journals Inc. (US)

Peripheral mechanisms	Central mechanisms
Alterations in sodium channel distribution and expression Alterations in calcium channel distribution and expression Changed neuropeptide expression Sympathetic sprouting Peripheral sensitization Changed peripheral circulation Axonal atrophy, degeneration or regeneration Small fibres injury Glycaemic flux	Central sensitization Aβ-fibre sprouting into lamina II of the dorsal horn Decreased inhibition via descending pathways

The risk factors of autonomic neuropathy and distal symmetric polyneuropathy:[18]

- Length of diabetes
- High blood glucose
- Arterial hypertension
- Peripheral artery disease (PAD)
- Mönckeberg's medial sclerosis
- Diabetic nephropathy and retinopathy
- Depression
- Truncal obesity
- Hypercholesterolemia
- Nicotine and/or alcohol misuse
- sedentary lifestyle
- Demographic factors (height, age, weight)

IV. Classification of Neuropathy

The different types of diabetic neuropathy (DN) can be grouped as follows:[19]

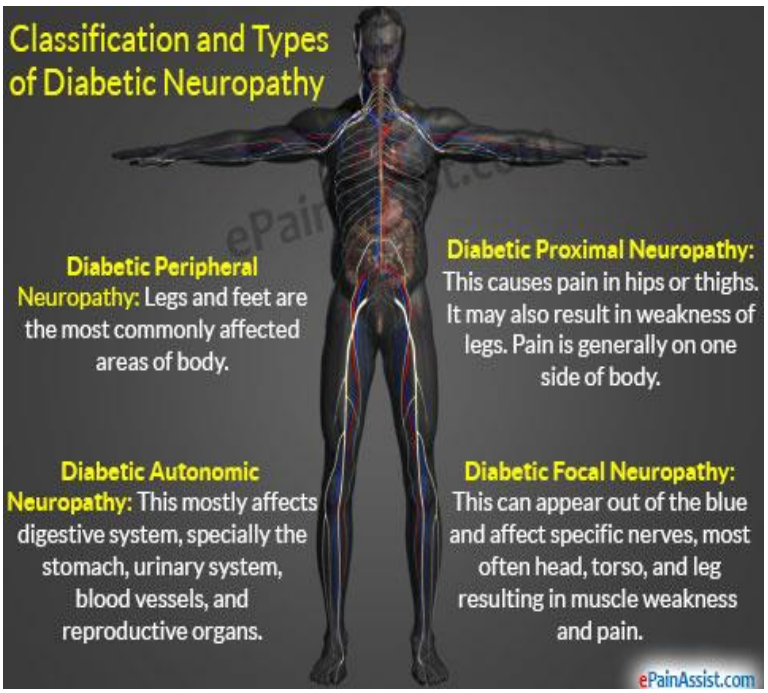
1. Anatomical distribution
   - Proximal or distal
   - Symmetric or asymmetric
   - Focal or multifocal or diffuse
2. Clinical course
   - Acute
   - Sub acute
   - Chronic
3. Characteristic main features
   - Aching or non-aching
   - Sensory
   - Motor, or autonomic
   - Pathophysiology

The most characteristic type of diabetic neuropathy is chronic distal symmetric polyneuropathy which account for around 75% of DNs and it was classified into typical or atypical according to their existence.20

There are four categories of diabetic neuropathy: [7 21]

- Peripheral neuropathy (moreover termed distal polyneuropathy and diabetic nerve pain)
- Proximal neuropathy (also named diabetic amyotrophy) can cause muscle weakness
- Autonomic neuropathy
- Focal neuropathy (also named mononeuropathy) it disturbs one precise nerve

Classification demonstrated in below diagram



© 2016 Global Journals Inc. (US)

Studies have revealed that reasonable intensity walking may not prompt augmented jeopardy of foot ulcers or re ulceration in peripheral neuropathic persons.[22] Autonomic neuropathy is also clearly connected with cardiovascular disease in diabetic's individuals.[23]

Essential Differential Diagnoses includes: [17]

- Medicines (such as cytostatic drugs)
- Toxins, metals(suchas alcohol)
- Kidney disorders
- Deficient Vitamin B (B1, B6, B12)
- Tumours, paraproteinemias
- Infections (such as Lyme disease ,HIV)
- Vasculitides
- Inherited neuropathies
- Endocrine illnesses (acromegaly, hypothyroidism)
- Immune neuropathies
- Impingement syndromes.

Diagnosis by exclusion should be based on laboratory test such as

- (CBC) Complete blood count
- Creatinine
- Vitamin B12
- Erythrocyte sedimentation rate (ESR)
- Alanine aminotransferase (ALAT)
- Thyroid-stimulating hormone (*TSH*)
- Gamma GT
- Folic acid
- immunoelectrophoresis.

V. Treatment for Neuropathic pain: [24]

1st drugs

- Tricyclic antidepressants (nortriptyline, amitriptyline, imipramine)
- Anticonvulsants (pregabalin, carbamazepine, gabapentin)
- SNRIs (venlafaxine, duloxetine)
- Topical Lidocaine

2nd drugs

- Tramadol
- Opioids (fentanyl, morphine)

3rd drugs

- Others anticonvulsants (topiramate, lamotrigine)
- NMDA (N-Methyl-D-aspartate) antagonists (memantine)
- Topical capsaicin
- GABAB (Gamma-aminobutyric acid B) receptor agonists [baclofen]
- SSRI

VI. Conclusion

The exact mechanisms creating DSP are unknown, yet are without a doubt depend on a number of factors and involve pathological changes due to reduced typical levels of blood glucose, the utmost noticeable of which includes augmented creation of free radicals due to hyperglycaemia-stimulated oxidative stress. The main demonstrated management that successfully defers the start or development of DSP is tight glycaemic control. However, DSP sooner or later precede in many diabetic's individuals in spite of good glycaemic control. Diabetes makes persons vulnerable to focal peripheral neuropathies including single nerves and nerve roots. The most recurrently affected cranial nerve is the oculomotor nerve which appears as incomplete oculomotor nerve palsy with pupillary sparing. Moreover, problem such as a unilateral truncal (thoracic) radiculopathy, display with acute abdominal or chest pain. Diabetes also leads to other peripheral nerve entrapments such as, median, ulnar, lateral femoral cutaneous, radial, and plantar nerves.[25]Despite the fact that it stays unsubstantiated whether tight glycaemic control can turn around pre-existing autonomic and peripheral nervous system injury brought on by type 1 diabetes, the sooner we perform intensive treatment, the more successfully we counteract future complications, involving neuropathy.[26]

References Références Referencias

1. Tracy JA, Engelstad JK, Dyck PJ. Microvasculitis in diabetic lumbosacral radiculoplexus neuropathy. J Clin Neuromuscul Dis. 2009; 11: 44–8.
2. Sinnreich M, Taylor BV, Dyck PJ. Diabetic neuropathies. Classification, clinical features, and pathophysiological basis. Neurologist. 2005; 11: 63–79.
3. Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic Neuropathies: A statement by the American Diabetes Association *Diabetes Care April 2005 28:4 956-962; doi:*10.2337/diacare.28.4.956
4. *Smith, B.H., Torrance, N. (2012). Epidemiology of neuropathic pain and its impact on quality of life. Curr Pain Headache Rep 16, 191–198.*
5. Diabetes Mellitus and Its Degenerative Complications: A Prospective Study of 4,400 Patients Observed Between 1947 and 1973 *Diabetes Care July/August 1978 1:4 252-263; doi:*10.2337/diacare.1.4.252
6. The Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of Intensive Therapy on the Microvascular Complications of Type 1 Diabetes Mellitus. *JAMA.* 2002; 287(19): 2563-2569. doi:10.1001/jama.287.19.2563.
7. Huizinga MM, Peltier A. Painful Diabetic Neuropathy: A Management-Centered Review *Clinical Diabetes January 2007 25: 1 6-15; doi:*10.2337/diaclin.25.1.6

© 2016 Global Journals Inc. (US)

8. *Rauck R, Makumi CW, Schwartz S, Graff O, Meno-Tetang G, Bell CF et al. A Randomized, Controlled Trial of Gabapentin Enacarbil in Subjects with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy. Pain Pract 2013; 13: 485–496*
9. Diabetic Neuropathies: The Nerve Damage of Diabetes|National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [Internet]. [cited 2016 Apr 9]. Available from: http://www.niddk.nih.gov/health-information/health-topics/Diabetes/diabetic-neuropathies-nerve-damage-diabetes/Pages/diabetic-neuropathies-nerve-damage.aspx
10. *Tesfaye S. Recent advances in the management of diabetic symmetrical polyneuropathy. J Diabetes Invest 2010; 2: 33–42.*
11. *Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care 2006; 29: 1518–1522.*
12. *Farvid MS, Homayooni F. Improving neuropathy scores in type 2 diabetic patients using micro-nutrients supplementation. J Diabetes 2011; 3: 260.*
13. R. Baron, A. Binder, G. Wasne Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment Lancet Neurol, 9 (2010), pp. 807–819.
14. Tesfaye S, Stephens L, Stephenson J, et al. The prevalence of diabetic neuropathy and its relation to glycemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 1996; 39: 1377–1384.
15. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic Autonomic Neuropathy. Diabetes Care [Internet]. 2003 May 1 [cited 2015 Nov 26]; 26(5): 1553–79. Available from: http://care.diabetesjournals.org/content/26/5/1553.full#cited-by
16. *Cameron NA, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. Diabetologia 2001; 44(11): 1973–1988.*
17. *Tesfaye S, Vileikyte L, Rayman G, et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev 2011; 27629–638.*
18. Ziegler D, Keller J, Maier C, Pannek J. Diabetic neuropathy. Exp Clin Endocrinol Diabetes. 2014 Jul 1; 122(7): 406-15.
19. Smith AG, Singleton JR. Diabetic neuropathy. Continuum. 2012; 18: 60–84. *This is an excellent and detailed review of DN*.
20. Bansal V, Kalita J, Misra UK. Diabetic neuropathy. Postgrad Med J. 2006; 82: 95–100.
21. Diabetic|Neuropathy|Classification|Types|Causes Risk Factors|Signs|Symptoms|Treatment [Internet]. [cited 2016 Apr 13]. Available from: http://www.epainassist.com/nerves/diabetic-neuropathy
22. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace CA. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. Medicine and Science in Sports and Exercise. 2003 Jul; 35(7): 1093-9.
23. Valensi P, Sachs R-N, Harfouche B, Lormeau B, Paries J, Cosson E, et al. Predictive Value of Cardiac Autonomic Neuropathy in Diabetic Patients With or Without Silent Myocardial Ischemia. Diabetes Care [Internet]. 2001 Feb 1; 24 (2): 339–43. Available from: http://care.diabetesjournals.org/content/24/2/339.abstract
24. Daniela Amorim. Pharmacological treatment of neuropathic pain: review of oral and topical therapy recommendations. IJCNMH 2015; 2:4.
25. Albers JW, Pop-Busui R. Diabetic neuropathy: mechanisms, emerging treatments, and subtypes. Current neurology and neuroscience reports. 2014 Aug 1; 14(8): 1-1.
26. Pop-Busui R, Herman WH, Feldman EL, et al. DCCT and EDIC Studies in Type 1 Diabetes: Lessons for Diabetic Neuropathy Regarding Metabolic Memory and Natural History. *Current diabetes reports*. 2010; 10(4): 276-282. doi:10.1007/s11892-010-0120-8.

© 2016 Global Journals Inc. (US)

Global Journal of Medical Research: F
Diseases
Volume 16 Issue 5 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Staphylococcus Associated Glomerulonephritis with IgA Mesangial Deposition

By Awad Magbri
Partners in Nephrology and Endocrinology (PINE), United States

Case- The case is that of 52 year Caucasian male with motor vehicle accident, status post open reduction and internal fixation of the left hip. He sustained wound infection with osteomyelitis due to multidrug resistant pseudomonas infection. Extensive debridement of the wound was carried out but the hardware was left in place. He underwent treatment with polymyxin antibiotic for a month then the course was complicated by renal failure which resolved with polymyxin dose adjustment. However, the hard ware was removed after 2 months of treatment. At that time wound culture revealed MRSA infection.

He received 4 weeks of Vancomycin and 6 week course of polymyxin after the hardware was removal. He was readmitted to the hospital with increasing pain and persistent drainage from the wound. Imagings were consistent with erosion of the femoral head with joint space loss, and septic arthritis with evidence of osteomyelitis and the presence of sinus tract to the skin surface. Wash out of the wound with debridement was carried out and another course of Vancomycin was instituted.

Keywords: staphylococcal associated glomerulonephritis, IgA nephropathy, hypocomplementemia, MRSA, endocapillary proliferation, mesangial staining.

GJMR-F Classification: NLMC Code: QW 161.5.S8

Strictly as per the compliance and regulations of:

© 2016. Awad Magbri. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Staphylococcus Associated Glomerulonephritis with IgA Mesangial Deposition

Awad Magbri

Keywords: staphylococcal associated glomerulonephritis, IgA nephropathy, hypocomplementemia, MRSA, endocapillary proliferation, mesangial staining.

I. Case

The case is that of 52 year Caucasian male with motor vehicle accident, status post open reduction and internal fixation of the left hip. He sustained wound infection with osteomyelitis due to multidrug resistant pseudomonas infection. Extensive debridement of the wound was carried out but the hardware was left in place. He underwent treatment with polymyxin antibiotic for a month then the course was complicated by renal failure which resolved with polymyxin dose adjustment. However, the hard ware was removed after 2 months of treatment. At that time wound culture revealed MRSA infection.

He received 4 weeks of Vancomycin and 6 week course of polymyxin after the hardware was removal. He was readmitted to the hospital with increasing pain and persistent drainage from the wound. Imagings were consistent with erosion of the femoral head with joint space loss, and septic arthritis with evidence of osteomyelitis and the presence of sinus tract to the skin surface. Wash out of the wound with debridement was carried out and another course of Vancomycin was instituted.

He developed worsening renal function with increasing creatinine from 1.2 to 6.7 mg/dl over 4 week period. His past medical history was positive for type II diabetes, hypertension, anemia, and hyperlipedemia. His medication consisted of insulin, lisinopril, iron, folic acid, omeprazole, and subcutaneous heparin. His review of system was positive for dark urine and leg swelling.

He was hypertensive on physical examination with BP 150/89 mmHg; afebrile and other wise examination of the cardiovascular, respiratory and abdomen were unremarkable. He had mild swelling of the left hip with surgical scar with chronic skin changes but no drainage. The examination also showed 3+ edema of the lower extremities.

His laboratory results showed WBC 11.4 with 73% PMN, Hg 7.8, and platelets of 332K. He had low albumin of 2.4 g/dl and phosphorus of 6.0 mg/dl. The serum creatinine had risen from 1.2 to 8.9 in 2 month's time. Urine protein was 2 gm/day and his UA showed protein >300 mg/dl, WBC 2-5, RBC packed, fine granular casts and RBC casts. His serology was negative for HIV, Hepatitis B and C, ANA, dsDNA, RF, ANCA.

His kidney biopsy revealed nodular mesangial sclerosis with necrotizing crescentic glomerulonephritis. The immunofluorescent (IF) staining of the kidney tissue showed 3+ IgA, 3+ C3. His complements C3, C4 were within normal limits and his urine immunofixation was negative.

Electron microscopy (EM) of renal specimen revealed deposition of immune-dense materials in the mesangium and in the subepithelia spaces. The final diagnosis was MRSA associated post-infectious glomerulonephritis.

Differential diagnoses: IgA nephropathy, post-infectious glomerulonephritis, pausi-immune ANCA associated nephritis, and MRSA post-infectious glomerulonephritis.

II. Discussion

There are 3 clinical settings for glomerulonephritis induced by Staphylococcus species; i- staphylococcal epidermidis bacteremia induced glomerulonephritis from ventricular-vascular shunts (1), ii- S aureus induced glomerulonephritis from endocarditis, and iii- Staphylococcal-associated glomerulonephritis (SAGN) which generally occurs by methicillin-resistant S aureus (MRSA) (2-9). MRSA induced glomerulonephritis resembles IgA nephropathy but a distinguished features of this form of nephritis is IgA-dominant or co-dominant mesangial staining with C3 deposition, Table-2. It is believed that Staphylococcal enterotoxins produced by MRSA act as superantigens, activating T-cells and inducing various cytokines which leads to this kind of glomerulonephritis. This antigen antibody reaction causes what is called "superantigen-related nephritis" (2). The antigen-antibody complexes deposit in the mesangium and sub-epithelium forming humps on electron microscopical examination. There are few reports on MRSA induced glomerulonephritis in the literature (7-9). Acute infectious glomerulonephritis is different when presented in adult patients.

The mean age of presentation is 49-58 years, and commonly associated with underlying co-

Author: MD, FACP, Dialysis Access Center of Pittsburgh.
e-mail: elmagbri@hotmail.com

© 2016 Global Journals Inc. (US)

morbidities in 40-50% of patients (10). These co-morbidities include alcoholism in 2-57%, diabetes in 8-29%, COPD in 7-33%, IV drug use in 3-27%, and malignancy in 5-10% (13) Table-1.

SAGN associated glomerulonephritis has protean manifestation including nephritic syndrome in 60%, nephrotic syndrome with gross proteinuria in 30-50%, the mean serum 24 hrs protein is 3.6 g/24 hrs which increases with increasing co-morbidities, and the mean serum creatinine in one series is 1.6-6.4 mg/dl, Table-1. The laboratory findings at the time of presentation are similar to those findings in other forms of glomerulonephritis (8). Hematuria in 98%, leuko-cytoria in 65%, mean protein excretion -3 g/day (21% had all features of nephrotic syndrome), and the mean serum creatinine at the time of biopsy – 5.1 mg/dl. Table-1

Kidney biopsy in these cases show Endocapillary proliferation in 70-100% of cases, crescents more than (20-30%) of the glomeruli in 14-36%, interstitial infiltration in 30-80%, and evidence of ATN in 20-40%.

Immunofluorescent staining showed granular staining and deposition of IgG and C3 or C3 alone in a peripheral capillary wall and mesangial distribution. IgA usually is absent or has less trace positivity on peripheral capillary walls (11). IF deposits are C3 in 93-100%, C1q in 18-35%, IgG in 55-65%, and IgM/IgA in 30-45% of cases, (11-18), Table-1.

The IF findings in this disease resemble those typically seen in patients with IgA nephropathy or Henoch-Schonlein purpura nephritis, however, the presence of hypocomplementemia, concurrent culture positive bacterial infection, and light microscopic pattern of diffuse Endocapillary hypercellularity with marked neutrophil infiltration in addition to mesangial and sub-endothelial deposits strongly favor acute post-infectious glomerulonephritis over IgA nephropathy, Table-2.

The EM study reveals mesangial deposits in 33-90%, sub-endothelial deposits in 44-75%, and sun-endothelial humps in 94-100% of cases (11).

The major diagnostic criteria should include at least 2 of the followings (11-13);

- Hypocomplementemia (primary low C3)
- Endocapillary proliferation and exudative glomerulonephritis on light microscopy.
- C3 dominant of co-dominant glomerular staining on IF microscopy. However, many of Staphylococcus-associated glomerulonephritis have IgA dominant or co-dominant disease together with C3 staining.
- Hump-shaped sub-epithelial deposits on EM.

The differential diagnoses of SAGN with hypocomplementemia in adults are;

- Infection associated glomerulonephritis
- Lupus nephritis
- Membrano-proliferative glomerulonephritis
- C3 glomerulonephritis
- Mixed cryoglobulinemia
- Athero-embolic disease which may presents with active urine sediment.

The presence of ANCA does not exclude the diagnosis of SAGN (11-13, 19-22).

III. Course of Disease and Prognosis

Successful eradication of the infection should result in resolution of GN. However, many patients with SAGN do not have complete resolution of the serum creatinine to baseline and will have persistent proteinuria. In one series (9) 50% of patients attained complete resolution of the disease. Older age and presence of co-morbid conditions like DM with high serum creatinine at presentation portend worse prognosis (8, 9).

In a study of 86 adults followed for 48 months in 41 patients without DM, 23/42(56%) attain complete remission, 11/41(27%) had persistent renal dysfunction, and 7/41(17%) progressed to ESRD requiring renal replacement therapy. The renal prognosis is worse in patients with DM among 11 patients with SAGN2/11 had persistent renal dysfunction and 9/11 progressed to ESRD (15, 23, 24).

In another report in elderly patients with SAGN (mean age 65 years) 34/109 were followed up for at least 3 months (11), 24% had complete recovery of renal function, 32% had persistent renal dysfunction, and 44% progressed to ESRD. Tubular atrophy and interstitial fibrosis are markers of chronic renal disease (11).

Table-1: Characteristics of staphylococcal associated glomerulonephritis

Characteristic	Percentage
Median age	49-50 years
Underlying disease	
• Alcoholism +/_ cirrhosis	2-57%
• Diabetes	8-29%
• COPD	7-33%
• IVDU	3-27%
• Malignancy	5-10%

© 2016 Global Journals Inc. (US)

Presentation	
• Nephritic syndrome	60%
• Nephrotic syndrome	30-50%
• Mean serum creatinine	1.5-6.4 mg/dl (increased with co-morbidities/crescentic GN)
• Mean 24 hr protein	3.6 g/24 hrs (increase with co-morbidities)
Kidney biopsy	
• Endocapillary proliferation	70-100%
• Crescents (>20-30%)	14-36%
• Interstitial infiltration	30-80%
• ATN	20-40%
IF staining:	
• C3 deposits	93-100%
• C1q	18-35%
• IgG deposits	55-65%
• IgM/IgA	30-45%
EM	
• Mesangial deposits	33-90%
• Sub-endothelial	44-75%
• Humps	94-100%
Sites of infection and microbiology	
• URI	24-44%
• SSTI	5-25%
• Lungs	16-18%
• Endocarditis	1-13%
• Dental	0-13%
• UTI	1-12%
Organisms	
• Streptococcus	14-47%
• Staphylococcus	12-24%
• Gram negative	1-22%
• No growth	24-59%

Table-2: differential from IgA nephropathy

Staphylococcal associated glomerulonephritis	IgA nephropathy
Older age at presentation with underlying DM	Younger age group with hematuria
Acute kidney injury at presentation	Can occurs when there is gross hematuria
Hypocomplementemia (mainly decrease C3)	Not typically seen
Diffuse exudative glomerulonephritis on LM	Mesangial proliferative disease
Stronger intensity of IF staining for C3 than IgA in glomerular deposits	Predominant global mesangial IgA staining
Sub-epithelial humps on EM	Mesangial deposits of IgA

References Références Referencias

1. Samtleben W, Bauriedal G, Bosch T, et al. Renal complications of infected shunts. Artif Organs 1993; 17: 695-701
2. Koyama A, Kobayashi M, Yamaguchi N, et al. Glomerulonephritis associated with MRSA infection: A possible role of bacterial superantigen. Kidney Int. 1995; 47: 207-216.
3. Nagaba Y, Hiki Y, Aoyama T, et al. Effective antibiotic treatment of methicillin-resistant Staphylococcus aureus-associated glomerulonephritis. Nephron. 2002; 92: 297-303
4. Yoh K, Kobayachi M, Hirayama A, et al. A case of superantigen-related glomerulonephritis after methicillin-resistant Staphylococcus aureus (MRSA) infection. Clin Nephrol. 1997; 48: 311-319.
5. Sato M, Nakazora H, Ofuji T. The pathogenetic role of Staphylococcus aureus in primary human glomerulonephritis. Clin Nephrol. 1979; 11: 190-195.
6. Montoliu J, Miro JM, Campistol JM, et al. Henoch-Schonlein purpura complicating Staphylococcal

© 2016 Global Journals Inc. (US)

endocarditis in heroin addict. Am J Nephrol. 1987; 7: 137-139.
7. Spector DA, Millan J, Zauber N, Burton J. Glomerulonephritis and Staphylococcal aureus infections. Clin Nephrol. 1980; 14: 256-261.
8. Handa T, Ono T, Watanabe H, et al. Glomerulonephritis induced by methicillin-sensitive Staphylococcus aureus infection. Clin Exp Nephrol. 2003; 7: 247-249.
9. Nasr SH, Markowitz GS, Whelan JD, et al. IgA-dominant acute post-staphylococcal glomerulonephritis complicating diabetic nephropathy. Hum Pathol. 2003; 34: 1235-1241.
10. Maroni G, Pozzi C, Guaglini S, et al. Long-term prognosis of diffuse proliferative glomerulonephritis associated with infection in adults. Nephrol Dial Transplant 2002; 17: 1204.
11. Nasr SH, Fidler ME, Valeri AM, et al. Postinfectious glomerulonephritis in the elderly. J Am Soc Nephrol 2011; 22: 187.
12. Nasr SH, Markowitz GS, Stokes MB, et al. Acute post-infectious glomerulonephritis in modern era: experience with 86 adults and review of the literature. Medicine (Baltimore) 2008; 87: 21.
13. Nasr SH, Radhakrishnan J, D'Agati VD. Bacterial infection-related glomerulonephritis in adults. Kidney Int 2013; 83: 792.
14. Wen YK, Chen ML. The significance of atypical morphology in the changes of spectrum of postinfectious glomerulonephritis. Clin Nephrol 2010; 73: 173.
15. Satoskar AA, Nadasdy G, Plaza JA, et al. Staphylococcus infection-associated glomerulonephritis mimicking IgA nephropathy. Clin J Am Soc Nephrol 2006; 1: 1179.
16. Sorger K, Gessler M, Hubner FK, et al. Follow-up studies of three subtypes of acute postinfectious glomerulonephritis ascertained by renal biopsy. Clin Nephrol 1987; 27: 111.
17. Nasr SH, D'Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. Nephron Clin Pract 2011; 119: c18
18. Worawichawong S, Girard L, Trpkov K, et al. immunoglobulin A-dominant postinfectious glomerulonephritis: frequent occurrence in nondiabetic patients with Staphylococcus aureus infection. Hum pathol 2011; 42: 279.
19. Choi HK, Lamprecht P, Niles JL, et al. Subacute bacterial endocarditis with positive cytoplasmic antineutrophil cytoplasmic antibodies and anti-proteinase 3 antibodies. Arthritis Rheum 2000; 43: 226
20. Chirinos JA, Corrales-Medina VF, Garcia S, et al. Endocarditis associated with antineutrophil cytoplasmic antibodies: a case report and review of the literature. Clin Rheumatol 2007; 26: 590.
21. Hanf W, Serre JE, Salmon JH, et al. Rapidly progressive ANCA positive glomerulonephritis as the presenting feature of infectious endocarditis. Rev Med Interne 2011; 32: e116
22. Boils CL, Nasr SH, Walker PD, et al. Update on endocarditis-associated glomerulonephritis. Kidney Int 2015; 87: 1241.
23. Monga G, Mazzucco G, di Belgiojoso GB, et al. Pattern of double glomerulopathies: a clinic-pathologic study of superimposed glomerulonephritis on diabetic glomerulosclerosis. Mod Pathol 1989; 2: 407.
24. Yum M, Maxwell DR, Hamburger R, Kleit SA. Primary glomerulonephritis complicating diabetic nephropathy: report of seven cases and review of the literature. Hum Pathol 1984; 15: 921.

© 2016 Global Journals Inc. (US)

Global Journals Inc. (US) Guidelines Handbook 2016

www.GlobalJournals.org

FELLOWS

FELLOW OF ASSOCIATION OF RESEARCH SOCIETY IN MEDICAL (FARSM)

Global Journals Incorporate (USA) is accredited by Open Association of Research Society (OARS), U.S.A and in turn, awards "FARSM" title to individuals.The 'FARSM' title is accorded to a selected professional after the approval of the Editor-in-Chief/Editorial Board Members/Dean.

- The "FARSM" is a dignified title which is accorded to a person's name viz. Dr. John E. Hall,Ph.D., FARSS or William Walldroff, M.S., FARSM.

FARSM accrediting is an honor. It authenticates your research activities. After recognition as FARSM, you can add 'FARSM' title with your name as you use this recognition as additional suffix to your status. This will definitely enhance and add more value and repute to your name. You may use it on your professional Counseling Materials such as CV, Resume, and Visiting Card etc.

The following benefits can be availed by you only for next three years from the date of certification:

FARSM designated members are entitled to avail a 40% discount while publishing their research papers (of a single author) with Global Journals Incorporation (USA), if the same is accepted by Editorial Board/Peer Reviewers. If you are a main author or co-author in case of multiple authors, you will be entitled to avail discount of 10%.

Once FARSM title is accorded, the Fellow is authorized to organize a symposium/seminar/conference on behalf of Global Journal Incorporation (USA). The Fellow can also participate in conference/seminar/symposium organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent.

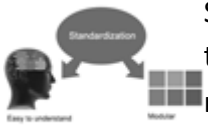
You may join as member of the Editorial Board of Global Journals Incorporation (USA) after successful completion of three years as Fellow and as Peer Reviewer. In addition, it is also desirable that you should organize seminar/symposium/conference at least once.

We shall provide you intimation regarding launching of e-version of journal of your stream time to time.This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

© Copyright by Global Journals Inc.(US) | Guidelines Handbook

The FARSM can go through standards of OARS. You can also play vital role if you have any suggestions so that proper amendment can take place to improve the same for the benefit of entire research community.

As FARSM, you will be given a renowned, secure and free professional email addres with 100 GB of space e.g. johnhall@globaljournals.org. This will include Webmail, Spam Assassin, Email Forwarders,Auto-Responders, Email Delivery Route tracing, etc.



The FARSM will be eligible for a free application of standardization of their researches. Standardization of research will be subject to acceptability within stipulated norms as the next step after publishing in a journal. We shall depute a team of specialized research professionals who will render their services for elevating your researches to next higher level, which is worldwide open standardization.

The FARSM member can apply for grading and certification of standards of their educational and Institutional Degrees to Open Association of Research, Society U.S.A. Once you are designated as FARSM, you may send us a scanned copy of all of you credentials. OARS will verify, grade and certify them. This will be based on your academic records, quality of research papers published by you, and some more criteria. After certification of all your credentials by OARS, they will be published on your Fellow Profile link on website https://associationofresearch.org which will be helpful to upgrade the dignity.

The FARSM members can avail the benefits of free research podcasting in Global Research Radio with their research documents. After publishing the work, (including published elsewhere worldwide with proper authorization) you can upload your research paper with your recorded voice or you can utilize chargeable services of our professional RJs to record your paper in their voice on request.

The FARSM member also entitled to get the benefits of free research podcasting of their research documents through video clips. We can also streamline your conference videos and display your slides/ online slides and online research video clips at reasonable charges, on request.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

The FARSM is eligible to earn from sales proceeds of his/her researches/reference/review Books or literature, while publishing with Global Journals. The FARSS can decide whether he/she would like to publish his/her research in a closed manner. In this case, whenever readers purchase that individual research paper for reading, maximum 60% of its profit earned as royalty by Global Journals, will be credited to his/her bank account. The entire entitled amount will be credited to his/her bank account exceeding limit of minimum fixed balance. There is no minimum time limit for collection. The FARSM member can decide its price and we can help in making the right decision.

The FARSM member is eligible to join as a paid peer reviewer at Global Journals Incorporation (USA) and can get remuneration of 15% of author fees, taken from the author of a respective paper. After reviewing 5 or more papers you can request to transfer the amount to your bank account.

MEMBER OF ASSOCIATION OF RESEARCH SOCIETY IN MEDICAL (MARSM)

The ' MARSM ' title is accorded to a selected professional after the approval of the Editor-in-Chief / Editorial Board Members/Dean.

The "MARSM" is a dignified ornament which is accorded to a person's name viz. Dr. John E. Hall, Ph.D., MARSM or William Walldroff, M.S., MARSM.

MARSM accrediting is an honor. It authenticates your research activities. Afterbecoming MARSM,you can add 'MARSM' title with your name as you use this recognition as additional suffix to your status. This will definitely enhance and add more value and repute to your name. You may use it on your professional Counseling Materials such as CV, Resume, Visiting Card and Name Plate etc.

The following benefitscan be availed by you only for next three years from the date of certification.

MARSM designated members are entitled to avail a 25% discount while publishing their research papers (of a single author) in Global Journals Inc., if the same is accepted by our Editorial Board and Peer Reviewers. If you are a main author or co-author of a group of authors, you will get discount of 10%.

As MARSM, you willbe given a renowned, secure and free professional email address with 30 GB of space e.g. johnhall@globaljournals.org. This will include Webmail, Spam Assassin, Email Forwarders,Auto-Responders, Email Delivery Route tracing, etc.

© Copyright by Global Journals Inc.(US) | Guidelines Handbook

We shall provide you intimation regarding launching of e-version of journal of your stream time to time.This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

The MARSM member can apply for approval, grading and certification of standards of their educational and Institutional Degrees to Open Association of Research, Society U.S.A.

Once you are designated as MARSM, you may send us a scanned copy of all of your credentials. OARS will verify, grade and certify them. This will be based on your academic records, quality of research papers published by you, and some more criteria.

It is mandatory to read all terms and conditions carefully.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

AUXILIARY MEMBERSHIPS

Institutional Fellow of Open Association of Research Society (USA) - OARS (USA)

Global Journals Incorporation (USA) is accredited by Open Association of Research Society, U.S.A (OARS) and in turn, affiliates research institutions as "Institutional Fellow of Open Association of Research Society" (IFOARS).

The "FARSC" is a dignified title which is accorded to a person's name viz. Dr. John E. Hall, Ph.D., FARSC or William Walldroff, M.S., FARSC.

The IFOARS institution is entitled to form a Board comprised of one Chairperson and three to five board members preferably from different streams. The Board will be recognized as "Institutional Board of Open Association of Research Society"-(IBOARS).

The Institute will be entitled to following benefits:

The IBOARS can initially review research papers of their institute and recommend them to publish with respective journal of Global Journals. It can also review the papers of other institutions after obtaining our consent. The second review will be done by peer reviewer of Global Journals Incorporation (USA) The Board is at liberty to appoint a peer reviewer with the approval of chairperson after consulting us.

The author fees of such paper may be waived off up to 40%.

The Global Journals Incorporation (USA) at its discretion can also refer double blind peer reviewed paper at their end to the board for the verification and to get recommendation for final stage of acceptance of publication.

The IBOARS can organize symposium/seminar/conference in their country on behalf of Global Journals Incorporation (USA)-OARS (USA). The terms and conditions can be discussed separately.

The Board can also play vital role by exploring and giving valuable suggestions regarding the Standards of "Open Association of Research Society, U.S.A (OARS)" so that proper amendment can take place for the benefit of entire research community. We shall provide details of particular standard only on receipt of request from the Board.

The board members can also join us as Individual Fellow with 40% discount on total fees applicable to Individual Fellow. They will be entitled to avail all the benefits as declared. Please visit Individual Fellow-sub menu of GlobalJournals.org to have more relevant details.

© Copyright by Global Journals Inc.(US) | Guidelines Handbook

We shall provide you intimation regarding launching of e-version of journal of your stream time to time. This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.

After nomination of your institution as "Institutional Fellow" and constantly functioning successfully for one year, we can consider giving recognition to your institute to function as Regional/Zonal office on our behalf.
The board can also take up the additional allied activities for betterment after our consultation.

The following entitlements are applicable to individual Fellows:

Open Association of Research Society, U.S.A (OARS) By-laws states that an individual Fellow may use the designations as applicable, or the corresponding initials. The Credentials of individual Fellow and Associate designations signify that the individual has gained knowledge of the fundamental concepts. One is magnanimous and proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice.

Open Association of Research Society (US)/ Global Journals Incorporation (USA), as described in Corporate Statements, are educational, research publishing and professional membership organizations. Achieving our individual Fellow or Associate status is based mainly on meeting stated educational research requirements.

Disbursement of 40% Royalty earned through Global Journals : Researcher = 50%, Peer Reviewer = 37.50%, Institution = 12.50% E.g. Out of 40%, the 20% benefit should be passed on to researcher, 15 % benefit towards remuneration should be given to a reviewer and remaining 5% is to be retained by the institution.

We shall provide print version of 12 issues of any three journals [as per your requirement] out of our 38 journals worth $ 2376 USD.

Other:

The individual Fellow and Associate designations accredited by Open Association of Research Society (US) credentials signify guarantees following achievements:

- The professional accredited with Fellow honor, is entitled to various benefits viz. name, fame, honor, regular flow of income, secured bright future, social status etc.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

- In addition to above, if one is single author, then entitled to 40% discount on publishing research paper and can get 10%discount if one is co-author or main author among group of authors.
- The Fellow can organize symposium/seminar/conference on behalf of Global Journals Incorporation (USA) and he/she can also attend the same organized by other institutes on behalf of Global Journals.
- The Fellow can become member of Editorial Board Member after completing 3yrs.
- The Fellow can earn 60% of sales proceeds from the sale of reference/review books/literature/publishing of research paper.
- Fellow can also join as paid peer reviewer and earn 15% remuneration of author charges and can also get an opportunity to join as member of the Editorial Board of Global Journals Incorporation (USA)
- • This individual has learned the basic methods of applying those concepts and techniques to common challenging situations. This individual has further demonstrated an in–depth understanding of the application of suitable techniques to a particular area of research practice.

Note :

"

- In future, if the board feels the necessity to change any board member, the same can be done with the consent of the chairperson along with anyone board member without our approval.
- In case, the chairperson needs to be replaced then consent of 2/3rd board members are required and they are also required to jointly pass the resolution copy of which should be sent to us. In such case, it will be compulsory to obtain our approval before replacement.
- In case of "Difference of Opinion [if any]" among the Board members, our decision will be final and binding to everyone.

"

Process of submission of Research Paper

The Area or field of specialization may or may not be of any category as mentioned in 'Scope of Journal' menu of the GlobalJournals.org website. There are 37 Research Journal categorized with Six parental Journals GJCST, GJMR, GJRE, GJMBR, GJSFR, GJHSS. For Authors should prefer the mentioned categories. There are three widely used systems UDC, DDC and LCC. The details are available as 'Knowledge Abstract' at Home page. The major advantage of this coding is that, the research work will be exposed to and shared with all over the world as we are being abstracted and indexed worldwide.

The paper should be in proper format. The format can be downloaded from first page of 'Author Guideline' Menu. The Author is expected to follow the general rules as mentioned in this menu. The paper should be written in MS-Word Format (*.DOC,*.DOCX).

The Author can submit the paper either online or offline. The authors should prefer online submission.Online Submission: There are three ways to submit your paper:

(A) (I) First, register yourself using top right corner of Home page then Login. If you are already registered, then login using your username and password.

(II) Choose corresponding Journal.

(III) Click 'Submit Manuscript'. Fill required information and Upload the paper.

(B) If you are using Internet Explorer, then Direct Submission through Homepage is also available.

(C) If these two are not conveninet , and then email the paper directly to dean@globaljournals.org.

Offline Submission: Author can send the typed form of paper by Post. However, online submission should be preferred.

Preferred Author Guidelines

MANUSCRIPT STYLE INSTRUCTION (Must be strictly followed)

Page Size: 8.27" X 11'"

- Left Margin: 0.65
- Right Margin: 0.65
- Top Margin: 0.75
- Bottom Margin: 0.75
- Font type of all text should be Swis 721 Lt BT.
- Paper Title should be of Font Size 24 with one Column section.
- Author Name in Font Size of 11 with one column as of Title.
- Abstract Font size of 9 Bold, "Abstract" word in Italic Bold.
- Main Text: Font size 10 with justified two columns section
- Two Column with Equal Column with of 3.38 and Gaping of .2
- First Character must be three lines Drop capped.
- Paragraph before Spacing of 1 pt and After of 0 pt.
- Line Spacing of 1 pt
- Large Images must be in One Column
- Numbering of First Main Headings (Heading 1) must be in Roman Letters, Capital Letter, and Font Size of 10.
- Numbering of Second Main Headings (Heading 2) must be in Alphabets, Italic, and Font Size of 10.

You can use your own standard format also.
Author Guidelines:

1. General,

2. Ethical Guidelines,

3. Submission of Manuscripts,

4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

1. GENERAL

Before submitting your research paper, one is advised to go through the details as mentioned in following heads. It will be beneficial, while peer reviewer justify your paper for publication.

Scope

The Global Journals Inc. (US) welcome the submission of original paper, review paper, survey article relevant to the all the streams of Philosophy and knowledge. The Global Journals Inc. (US) is parental platform for Global Journal of Computer Science and Technology, Researches in Engineering, Medical Research, Science Frontier Research, Human Social Science, Management, and Business organization. The choice of specific field can be done otherwise as following in Abstracting and Indexing Page on this Website. As the all Global

Journals Inc. (US) are being abstracted and indexed (in process) by most of the reputed organizations. Topics of only narrow interest will not be accepted unless they have wider potential or consequences.

2. ETHICAL GUIDELINES

Authors should follow the ethical guidelines as mentioned below for publication of research paper and research activities.

Papers are accepted on strict understanding that the material in whole or in part has not been, nor is being, considered for publication elsewhere. If the paper once accepted by Global Journals Inc. (US) and Editorial Board, will become the copyright of the Global Journals Inc. (US).

Authorship: The authors and coauthors should have active contribution to conception design, analysis and interpretation of findings. They should critically review the contents and drafting of the paper. All should approve the final version of the paper before submission

The Global Journals Inc. (US) follows the definition of authorship set up by the Global Academy of Research and Development. According to the Global Academy of R&D authorship, criteria must be based on:

1) Substantial contributions to conception and acquisition of data, analysis and interpretation of the findings.

2) Drafting the paper and revising it critically regarding important academic content.

3) Final approval of the version of the paper to be published.

All authors should have been credited according to their appropriate contribution in research activity and preparing paper. Contributors who do not match the criteria as authors may be mentioned under Acknowledgement.

Acknowledgements: Contributors to the research other than authors credited should be mentioned under acknowledgement. The specifications of the source of funding for the research if appropriate can be included. Suppliers of resources may be mentioned along with address.

Appeal of Decision: The Editorial Board's decision on publication of the paper is final and cannot be appealed elsewhere.

Permissions: It is the author's responsibility to have prior permission if all or parts of earlier published illustrations are used in this paper.

Please mention proper reference and appropriate acknowledgements wherever expected.

If all or parts of previously published illustrations are used, permission must be taken from the copyright holder concerned. It is the author's responsibility to take these in writing.

Approval for reproduction/modification of any information (including figures and tables) published elsewhere must be obtained by the authors/copyright holders before submission of the manuscript. Contributors (Authors) are responsible for any copyright fee involved.

3. SUBMISSION OF MANUSCRIPTS

Manuscripts should be uploaded via this online submission page. The online submission is most efficient method for submission of papers, as it enables rapid distribution of manuscripts and consequently speeds up the review procedure. It also enables authors to know the status of their own manuscripts by emailing us. Complete instructions for submitting a paper is available below.

Manuscript submission is a systematic procedure and little preparation is required beyond having all parts of your manuscript in a given format and a computer with an Internet connection and a Web browser. Full help and instructions are provided on-screen. As an author, you will be prompted for login and manuscript details as Field of Paper and then to upload your manuscript file(s) according to the instructions.

To avoid postal delays, all transaction is preferred by e-mail. A finished manuscript submission is confirmed by e-mail immediately and your paper enters the editorial process with no postal delays. When a conclusion is made about the publication of your paper by our Editorial Board, revisions can be submitted online with the same procedure, with an occasion to view and respond to all comments.

Complete support for both authors and co-author is provided.

4. MANUSCRIPT'S CATEGORY

Based on potential and nature, the manuscript can be categorized under the following heads:

Original research paper: Such papers are reports of high-level significant original research work.

Review papers: These are concise, significant but helpful and decisive topics for young researchers.

Research articles: These are handled with small investigation and applications

Research letters: The letters are small and concise comments on previously published matters.

5.STRUCTURE AND FORMAT OF MANUSCRIPT

The recommended size of original research paper is less than seven thousand words, review papers fewer than seven thousands words also.Preparation of research paper or how to write research paper, are major hurdle, while writing manuscript. The research articles and research letters should be fewer than three thousand words, the structure original research paper; sometime review paper should be as follows:

Papers: These are reports of significant research (typically less than 7000 words equivalent, including tables, figures, references), and comprise:

(a)Title should be relevant and commensurate with the theme of the paper.

(b) A brief Summary, "Abstract" (less than 150 words) containing the major results and conclusions.

(c) Up to ten keywords, that precisely identifies the paper's subject, purpose, and focus.

(d) An Introduction, giving necessary background excluding subheadings; objectives must be clearly declared.

(e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition; sources of information must be given and numerical methods must be specified by reference, unless non-standard.

(f) Results should be presented concisely, by well-designed tables and/or figures; the same data may not be used in both; suitable statistical data should be given. All data must be obtained with attention to numerical detail in the planning stage. As reproduced design has been recognized to be important to experiments for a considerable time, the Editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned un-refereed;

(g) Discussion should cover the implications and consequences, not just recapitulating the results; conclusions should be summarizing.

(h) Brief Acknowledgements.

(i) References in the proper form.

Authors should very cautiously consider the preparation of papers to ensure that they communicate efficiently. Papers are much more likely to be accepted, if they are cautiously designed and laid out, contain few or no errors, are summarizing, and be conventional to the approach and instructions. They will in addition, be published with much less delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and to make suggestions to improve briefness.

It is vital, that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

Format

Language: The language of publication is UK English. Authors, for whom English is a second language, must have their manuscript efficiently edited by an English-speaking person before submission to make sure that, the English is of high excellence. It is preferable, that manuscripts should be professionally edited.

Standard Usage, Abbreviations, and Units: Spelling and hyphenation should be conventional to The Concise Oxford English Dictionary. Statistics and measurements should at all times be given in figures, e.g. 16 min, except for when the number begins a sentence. When the number does not refer to a unit of measurement it should be spelt in full unless, it is 160 or greater.

Abbreviations supposed to be used carefully. The abbreviated name or expression is supposed to be cited in full at first usage, followed by the conventional abbreviation in parentheses.

Metric SI units are supposed to generally be used excluding where they conflict with current practice or are confusing. For illustration, 1.4 l rather than 1.4 × 10-3 m3, or 4 mm somewhat than 4 × 10-3 m. Chemical formula and solutions must identify the form used, e.g. anhydrous or hydrated, and the concentration must be in clearly defined units. Common species names should be followed by underlines at the first mention. For following use the generic name should be constricted to a single letter, if it is clear.

Structure

All manuscripts submitted to Global Journals Inc. (US), ought to include:

Title: The title page must carry an instructive title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) wherever the work was carried out. The full postal address in addition with the e-mail address of related author must be given. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining and indexing.

Abstract, used in Original Papers and Reviews:

Optimizing Abstract for Search Engines

Many researchers searching for information online will use search engines such as Google, Yahoo or similar. By optimizing your paper for search engines, you will amplify the chance of someone finding it. This in turn will make it more likely to be viewed and/or cited in a further work. Global Journals Inc. (US) have compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Key Words

A major linchpin in research work for the writing research paper is the keyword search, which one will employ to find both library and Internet resources.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy and planning a list of possible keywords and phrases to try.

Search engines for most searches, use Boolean searching, which is somewhat different from Internet searches. The Boolean search uses "operators," words (and, or, not, and near) that enable you to expand or narrow your affords. Tips for research paper while preparing research paper are very helpful guideline of research paper.

Choice of key words is first tool of tips to write research paper. Research paper writing is an art.A few tips for deciding as strategically as possible about keyword search:

- One should start brainstorming lists of possible keywords before even begin searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in research paper?" Then consider synonyms for the important words.
- It may take the discovery of only one relevant paper to let steer in the right keyword direction because in most databases, the keywords under which a research paper is abstracted are listed with the paper.
- One should avoid outdated words.

Keywords are the key that opens a door to research work sources. Keyword searching is an art in which researcher's skills are bound to improve with experience and time.

Numerical Methods: Numerical methods used should be clear and, where appropriate, supported by references.

Acknowledgements: Please make these as concise as possible.

References

References follow the Harvard scheme of referencing. References in the text should cite the authors' names followed by the time of their publication, unless there are three or more authors when simply the first author's name is quoted followed by et al. unpublished work has to only be cited where necessary, and only in the text. Copies of references in press in other journals have to be supplied with submitted typescripts. It is necessary that all citations and references be carefully checked before submission, as mistakes or omissions will cause delays.

References to information on the World Wide Web can be given, but only if the information is available without charge to readers on an official site. Wikipedia and Similar websites are not allowed where anyone can change the information. Authors will be asked to make available electronic copies of the cited information for inclusion on the Global Journals Inc. (US) homepage at the judgment of the Editorial Board.

The Editorial Board and Global Journals Inc. (US) recommend that, citation of online-published papers and other material should be done via a DOI (digital object identifier). If an author cites anything, which does not have a DOI, they run the risk of the cited material not being noticeable.

The Editorial Board and Global Journals Inc. (US) recommend the use of a tool such as Reference Manager for reference management and formatting.

Tables, Figures and Figure Legends

Tables: Tables should be few in number, cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g. Table 4, a self-explanatory caption and be on a separate sheet. Vertical lines should not be used.

Figures: Figures are supposed to be submitted as separate files. Always take in a citation in the text for each figure using Arabic numbers, e.g. Fig. 4. Artwork must be submitted online in electronic form by e-mailing them.

Preparation of Electronic Figures for Publication

Even though low quality images are sufficient for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit (or e-mail) EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Do not use pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings) in relation to the imitation size. Please give the data for figures in black and white or submit a Color Work Agreement Form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution (at final image size) ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs) : >350 dpi; figures containing both halftone and line images: >650 dpi.

Color Charges: It is the rule of the Global Journals Inc. (US) for authors to pay the full cost for the reproduction of their color artwork. Hence, please note that, if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a color work agreement form before your paper can be published.

Figure Legends: Self-explanatory legends of all figures should be incorporated separately under the heading 'Legends to Figures'. In the full-text online edition of the journal, figure legends may possibly be truncated in abbreviated links to the full screen version. Therefore, the first 100 characters of any legend should notify the reader, about the key aspects of the figure.

6. AFTER ACCEPTANCE

Upon approval of a paper for publication, the manuscript will be forwarded to the dean, who is responsible for the publication of the Global Journals Inc. (US).

6.1 Proof Corrections

The corresponding author will receive an e-mail alert containing a link to a website or will be attached. A working e-mail address must therefore be provided for the related author.

Acrobat Reader will be required in order to read this file. This software can be downloaded

(Free of charge) from the following website:

www.adobe.com/products/acrobat/readstep2.html. This will facilitate the file to be opened, read on screen, and printed out in order for any corrections to be added. Further instructions will be sent with the proof.

Proofs must be returned to the dean at dean@globaljournals.org within three days of receipt.

As changes to proofs are costly, we inquire that you only correct typesetting errors. All illustrations are retained by the publisher. Please note that the authors are responsible for all statements made in their work, including changes made by the copy editor.

6.2 Early View of Global Journals Inc. (US) (Publication Prior to Print)

The Global Journals Inc. (US) are enclosed by our publishing's Early View service. Early View articles are complete full-text articles sent in advance of their publication. Early View articles are absolute and final. They have been completely reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are in final form, no changes can be made after sending them. The nature of Early View articles means that they do not yet have volume, issue or page numbers, so Early View articles cannot be cited in the conventional way.

6.3 Author Services

Online production tracking is available for your article through Author Services. Author Services enables authors to track their article - once it has been accepted - through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production. The authors will receive an e-mail with a unique link that enables them to register and have their article automatically added to the system. Please ensure that a complete e-mail address is provided when submitting the manuscript.

6.4 Author Material Archive Policy

Please note that if not specifically requested, publisher will dispose off hardcopy & electronic information submitted, after the two months of publication. If you require the return of any information submitted, please inform the Editorial Board or dean as soon as possible.

6.5 Offprint and Extra Copies

A PDF offprint of the online-published article will be provided free of charge to the related author, and may be distributed according to the Publisher's terms and conditions. Additional paper offprint may be ordered by emailing us at: editor@globaljournals.org .

Before start writing a good quality Computer Science Research Paper, let us first understand what is Computer Science Research Paper? So, Computer Science Research Paper is the paper which is written by professionals or scientists who are associated to Computer Science and Information Technology, or doing research study in these areas. If you are novel to this field then you can consult about this field from your supervisor or guide.

TECHNIQUES FOR WRITING A GOOD QUALITY RESEARCH PAPER:

1. Choosing the topic: In most cases, the topic is searched by the interest of author but it can be also suggested by the guides. You can have several topics and then you can judge that in which topic or subject you are finding yourself most comfortable. This can be done by asking several questions to yourself, like Will I be able to carry our search in this area? Will I find all necessary recourses to accomplish the search? Will I be able to find all information in this field area? If the answer of these types of questions will be "Yes" then you can choose that topic. In most of the cases, you may have to conduct the surveys and have to visit several places because this field is related to Computer Science and Information Technology. Also, you may have to do a lot of work to find all rise and falls regarding the various data of that subject. Sometimes, detailed information plays a vital role, instead of short information.

2. Evaluators are human: First thing to remember that evaluators are also human being. They are not only meant for rejecting a paper. They are here to evaluate your paper. So, present your Best.

3. Think Like Evaluators: If you are in a confusion or getting demotivated that your paper will be accepted by evaluators or not, then think and try to evaluate your paper like an Evaluator. Try to understand that what an evaluator wants in your research paper and automatically you will have your answer.

4. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

5. Ask your Guides: If you are having any difficulty in your research, then do not hesitate to share your difficulty to your guide (if you have any). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work then ask the supervisor to help you with the alternative. He might also provide you the list of essential readings.

6. Use of computer is recommended: As you are doing research in the field of Computer Science, then this point is quite obvious.

7. Use right software: Always use good quality software packages. If you are not capable to judge good software then you can lose quality of your paper unknowingly. There are various software programs available to help you, which you can get through Internet.

8. Use the Internet for help: An excellent start for your paper can be by using the Google. It is an excellent search engine, where you can have your doubts resolved. You may also read some answers for the frequent question how to write my research paper or find model research paper. From the internet library you can download books. If you have all required books make important reading selecting and analyzing the specified information. Then put together research paper sketch out.

9. Use and get big pictures: Always use encyclopedias, Wikipedia to get pictures so that you can go into the depth.

10. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right! It is a good habit, which helps to not to lose your continuity. You should always use bookmarks while searching on Internet also, which will make your search easier.

11. Revise what you wrote: When you write anything, always read it, summarize it and then finalize it.

12. Make all efforts: Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

13. Have backups: When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

14. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

15. Use of direct quotes: When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

16. Use proper verb tense: Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

17. Never use online paper: If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

18. Pick a good study spot: To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

19. Know what you know: Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

20. Use good quality grammar: Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

21. Arrangement of information: Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

22. Never start in last minute: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

23. Multitasking in research is not good: Doing several things at the same time proves bad habit in case of research activity. Research is an area, where everything has a particular time slot. Divide your research work in parts and do particular part in particular time slot.

24. Never copy others' work: Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. Take proper rest and food: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. Go for seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

27. Refresh your mind after intervals: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. Make colleagues: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. Think technically: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. Think and then print: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

32. Never oversimplify everything: To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.

Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

· Shun use of extra pictures - include only those figures essential to presenting results

Title Page:

Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

Procedures (Methods and Materials):

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

Please carefully note down following rules and regulation before submitting your Research Paper to Global Journals Inc. (US):

Segment Draft and Final Research Paper: You have to strictly follow the template of research paper. If it is not done your paper may get rejected.

- The **major constraint** is that you must independently make all content, tables, graphs, and facts that are offered in the paper. You must write each part of the paper wholly on your own. The Peer-reviewers need to identify your own perceptive of the concepts in your own terms. NEVER extract straight from any foundation, and never rephrase someone else's analysis.

- Do not give permission to anyone else to "PROOFREAD" your manuscript.

- Methods to avoid Plagiarism is applied by us on every paper, if found guilty, you will be blacklisted by all of our collaborated research groups, your institution will be informed for this and strict legal actions will be taken immediately.)
- To guard yourself and others from possible illegal use please do not permit anyone right to use to your paper and files.

© Copyright by Global Journals Inc.(US)| Guidelines Handbook

Criterion for Grading a Research Paper (Compilation) by Global Journals Inc. (US)

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals Inc. (US).

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

A

Adenocarcinoma · 26, 29
Aetiological · 23
Angiotensin · 1
Arthralgia · 2

C

Cobblestoning · 27
Cyclophosphamide · 2

E

Erlotinib · 26, 27, 28, 29

G

Glomerulitis · 2
Glomerulonephritis · 21

H

Hypocalcemia · 23

I

Isothiocyanates · 34, 35

M

Macroglobulinema · 39
Myoglobuinuria · 21

N

Nephrotic · 21
Nodosa · 1

O

Oliguric · 21
Onyiora · 4
Onyiorah · 5, 8
Orchitis · 2, 3

P

Papilledema · 1
Phytochemicals · 34
Pneumocyte · 28
Pneumonitis · 26, 27, 28, 29, 30
Polyneuropathy · 2
Proteinuria · 21

R

Rahbdomyolysis · 21

W

Waldenstrom's · 39

save our planet

Global Journal of Medical Research

Visit us on the Web at www.GlobalJournals.org | www.MedicalResearchJournal.org
or email us at helpdesk@globaljournals.org

ISSN 9755896

© Global Journals