Erlotinib Induced Fatal Estimation of New Drug 
Polyarteritis Nodosa Renal Crisis Waldenstrom’s Macroglobulinema

Diseases
Cancer, Ophthalmology & Pediatric

Discovering Thoughts, Inventing Future

VOLUME 16 ISSUE 5 VERSION 1.0

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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

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Polyarteritis Nodosa Renal Crisis with Malignant Hypertension

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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/M² monthly IV for 6 months.
- Hypertension became controlled, average BP 132/80 mmHg within 2-3 weeks.
- The patient was initially stabilized with IV nitroprusside 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

Polyarteritis 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 hyperendemic 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 polyangiitis (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 (indictative of glomerulitis are usually absent (1,11).

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

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.

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Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

By Okeh UM & Oyeka ICA
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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
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1. 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
samples of subjects of equal sizes $n_1$. In the second phase 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-priori 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 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 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. If the study is a retrospective one then the required data would of course be obtained from case history files of the study participants.

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

\[
  u_{ix} = \begin{cases} 
 1, & \text{if the } i\text{th subject tested, screened or administered a new drug by evaluation committee } X \text{ responds positive} \\
 0, & \text{otherwise}
  \end{cases}
\]

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

Let

\[
  \pi_x^+ = P(u_{ix} = 1)
\]

Also define

\[
  W_x = \sum_{i=1}^{n_i} u_{ix}
\]

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

\[
  E(u_{ix}) = \pi_x^+; Var(u_{ix}) = \pi_x^+(1 - \pi_x^+),
\]

Also the expected value and variance of $W_x$ are respectively.

\[
  E W_x = \sum_{i=1}^{n_i} E u_{ix} = n_i \pi_x^+; Var W_x = \sum_{i=1}^{n_i} Var u_{ix} = n_i \pi_x^+ - \pi_x^+
\]
Now $\pi^+_X$ is the proportion on probability that on the average subjects tested, screened or treated by evaluation committee X responds positive. Its sample estimate is

$$\hat{\pi}^+_X = P_X = \frac{W_X}{n_1} = \frac{f^+_X}{n_1}$$

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

$$Var(\hat{\pi}^+_X) = Var\left(\frac{W_X}{n_1}\right) = \frac{\hat{\pi}^+_X(1-\hat{\pi}^+_X)}{n_1}$$

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

$$H_0 : \pi^+_X \leq \pi_{xo} \; versus \; H_1 : \pi^+_X > \pi_{xo} \; (0 \leq \pi_{xo} \leq 1)$$

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

$$\chi^2 = \frac{(W_X - n_1 \cdot \pi_{xo})^2}{Var(W_X)} = \frac{n_1 \left(\hat{\pi}^+_X - \pi_{xo}\right)^2}{\hat{\pi}^+_X \left(1 - \hat{\pi}^+_X\right)}$$

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 $\alpha$ level of significance if

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

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

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

for $i=1,2,…,n$.

Let

$$\pi^+_Y = P(u_{iy} = 1)$$

And

$$W_Y = \sum_{i=1}^{n_1} u_{iy}$$

Now

$$E(u_{iy}) = \pi^+_Y; Var(u_{iy}) = \pi^+_Y(1-\pi^+_Y)$$

And

$$E(W_Y) = n_1 \cdot \pi^+_Y; Var(W_Y) = n_1 \cdot \pi^+_Y(1-\pi^+_Y)$$

For evaluation committee Y approved agency, $\pi^+_Y$ 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
\[ \hat{\pi}_y^+ = p_y = \frac{W_y}{n_1} = \frac{f_y^+}{n_1} \]

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 \( u_{iy} \), \( i = 1, 2, \ldots, n_1 \).

The corresponding sample variance is

\[
\text{Var} (\hat{\pi}_y^+) = \frac{\text{Var}(W_y)}{n_1^2} = \frac{\hat{\pi}_y^+(1 - \hat{\pi}_y^+)}{n_1} \tag{17}
\]

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 \( \pi_z^+ \) for evaluation committee agency \( Z \) as

\[ \hat{\pi}_z^+ = p_z = \frac{W_z}{n_1} = \frac{f_z^+}{n_1} \tag{18} \]

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

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

for \( i = 1, 2, \ldots, n_x \)

Let

\[ \pi_{yx}^+ = P(u_{iy,x} = 1) \tag{20} \]

And

\[ W_{y,x} = \sum_{i=1}^{n_{y,x}} u_{iy,x} \tag{21} \]

The expected value and variance of \( u_{iy,x} \) are respectively

\[ E(u_{iy,x}) = \pi_{yx}^+; \text{Var}(u_{iy,x}) = \pi_{yx}^+(1 - \pi_{yx}^+) \tag{22} \]

Also the expected value and variance of \( W_{y,x} \) are respectively

\[ E(W_{y,x}) = \sum_{i=1}^{n_{y,x}} E(u_{iy,x}) = n_{y,x}\pi_{yx}^+; \text{Var}(W_{y,x}) = \sum_{i=1}^{n_{y,x}} \text{Var}(u_{iy,x}) = n_{y,x}\pi_{yx}^+(1 - \pi_{yx}^+) \tag{23} \]

Now \( \pi_{yx}^+ \) 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
positive given that the corresponding subjects tested by evaluation committee X have also responded positive to the new drug product. Its sample estimate is

$$\pi_{yx}^+ = p_{yx} = \frac{W_{yx}}{n_{yx}} = \frac{f_{yx}^+}{n_{yx}}$$

Where $f_{yx}^+$ 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 $f_{yx}$ is the total number of 1s in the frequency distribution of the $n_{yx}$ values of 0s and 1s in $u_{yx}$ for $i=1,2,...,n_x$.

The sample variance of $\hat{\pi}_{yx}$ is from Equation 23

$$\text{Var}(\hat{\pi}_{yx}) = \frac{\text{Var}(W_{yx})}{n_y^2} = \frac{\hat{\pi}_{yx}(1-\hat{\pi}_{yx})}{n_x}$$

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 $\pi_{yx}$, that is the null hypothesis

$$H_0 : \pi_{yx}^+ \geq \pi_{yx}, \quad H_1 : \pi_{yx}^+ < \pi_{yx}, (0 \leq \pi_{yx} \leq 1)$$

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

$$\chi^2 = \frac{(W_{yx} - n_x\pi_{yx})^2}{\text{Var}(W_{yx})} = \frac{n_x(\hat{\pi}_{yx} - \pi_{yx})^2}{\hat{\pi}_{yx}(1-\hat{\pi}_{yx})}$$

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 $\alpha$ 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

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

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

Let

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

And

$$W_{z,x} = \sum_{i=1}^{n_x} u_{iz,x}$$

Now

$$E(u_{iz,x}) = \pi_{z,x}^+ ; \text{Var}(u_{iz,x}) = \pi_{z,x}^+ (1-\pi_{z,x}^+)$$

And

$$E(W_{z,x}) = n_{z,x} \cdot \pi_{z,x}^+ ; \text{Var}(W_{z,x}) = n_{z,x} \cdot \pi_{z,x}^+ (1-\pi_{z,x}^+)$$

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Note that $\pi_{y,xz}^+$ 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

$$\hat{\pi}_{y,xz}^+ = P_{y,xz} = \frac{W_{y,xz}}{n_{y,xz}} = \frac{f_{y,xz}^+}{n_{y,xz}}$$

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 $u_{y,xz}, i = 1, 2, ..., n_{y,xz}$.

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

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

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

$$\hat{\pi}_{x,yz}^+ = P_{x,yz} = \frac{W_{x,yz}}{N_{x,yz}} = \frac{f_{x,yz}^+}{n_{x,yz}}$$

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

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

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

$$\hat{\pi}_{z,xy}^+ = P_{z,xy}^+ = \hat{\pi}_{y,xz}^+ = P_{y,xz}^+ and \hat{\pi}_{x,yz}^+ = P_{x,yz}^+$$

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

$$\frac{1}{P(AB)} > \frac{1}{P(AC)}$$

Hence

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

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

$$P(C/AB) > P(B/AC).$$
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, 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.

Nonetheless 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 $\overline{A\bar{B}}/C$ which is

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

OR

In terms of estimated probabilities,

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

$$P(A) = a = P_x; P(B) = b = P_y; P(C) = c = P_z$$

And

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

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

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

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

$$P(S_2) = P_xP_{y.x} + P_xP_{z.x} + P_yP_{z.y} - 2P_{z.xy} P_{y.x} P_x$$

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 $S_3 = (ABC, AB\bar{C}, \bar{A}BC)$ whose sample estimate is

$$P(S_3) = P_xP_{y.x} + P_xP_{z.x} - P_{z.xy}P_{y.x}P_x$$

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

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

which when expressed in terms of sample probabilities becomes
Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

The probability that none of the evaluation committees approves a drug or product for use is the probability of the event \( S_0 = (\overline{ABC}) \) which is

\[
P(S_0) = P(\overline{ABC}) = 1 - \left( P(A) + P(B) + P(C) - P(B|A).P(A) - P(C|A).P(A) - P(C|B).P(B) + P(ABC) \right)
\]

Which when evaluated in terms of sampled estimates becomes

\[
P(S_0) = 1 - \left( P_x + P_y + P_z - P_x.P_y.P_z - P_x.P_z.P_y - P_x.P_y.P_z + P_x.P_y.P_z \right)
\]

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

<table>
<thead>
<tr>
<th>S/No</th>
<th>Event</th>
<th>Approval Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( ABC )</td>
<td>( P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>2</td>
<td>( ABC )</td>
<td>( P_{x}.P_{y}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>3</td>
<td>( \overline{ABC} )</td>
<td>( P_{x}.P_{y}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>4</td>
<td>( \overline{ABC} )</td>
<td>( P_{x} - P_{x}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>5</td>
<td>( \overline{ABC} )</td>
<td>( P_{y}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>6</td>
<td>( \overline{ABC} )</td>
<td>( P_{y}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>7</td>
<td>( \overline{ABC} )</td>
<td>( P_{z} - P_{x}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>8</td>
<td>( \overline{ABC} )</td>
<td>( 1 - \left( P_x + P_y + P_z - P_x.P_y.P_z - P_x.P_z.P_y - P_x.P_y.P_z + P_x.P_y.P_z \right) )</td>
</tr>
<tr>
<td>9</td>
<td>( S_x(\text{at least two Evaluation committees}) )</td>
<td>( P_{x}.P_{y}.P_{z,xy} + P_{x}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>10</td>
<td>( S_x(\text{Evaluation Committee X ; and at least one other}) )</td>
<td>( P_{x}.P_{y}.P_{z,xy} + P_{x}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>11</td>
<td>( S_y(\text{Evaluation Committee Y and at least one other}) )</td>
<td>( P_{x}.P_{y}.P_{z,xy} + P_{x}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
</tr>
<tr>
<td>12</td>
<td>( S_z(\text{Evaluation Committee Z and at least one other}) )</td>
<td>( P_{x}.P_{y}.P_{z,xy} + P_{x}.P_{z,xy} - P_{z,xy}.P_{y,x}.P_x )</td>
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</table>

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

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<tr>
<th>S/No</th>
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\[ n_i \] = 40

\[ f_i^+(x) = 23(f_i^+(x)) \]
\[ f_i^+(x) = 22(f_i^+(x)) \]
\[ f_i^+(x) = 22(f_i^+(x)) \]

\[ \hat{\pi}_i^+ = 0.575(\hat{\pi}_i^+) \]
\[ \hat{\pi}_i^+ = 0.550(\hat{\pi}_i^+) \]
\[ \hat{\pi}_i^+ = 0.550(\hat{\pi}_i^+) \]

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

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<th>Matched Pair Team 1</th>
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Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

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\[
\hat{\pi}_{k,j} = \frac{n_{k,j}}{12(n_{y,x})} + 0.333(\hat{\pi}_{y,x})
\]

\[
f_{k,j} = 4(f_{y,x}^{+}) + 0.556(\hat{f}_{y,x}^{+})
\]

\[
\hat{\pi}_{k,j} = \frac{18(n_{z,x})}{16(n_{z,y})} + 0.688(\hat{\pi}_{z,x})
\]

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

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<td>18</td>
<td>R</td>
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<td>R</td>
</tr>
<tr>
<td>25</td>
<td>N</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

\[
n_{k,j} = 8(n_{x,y}) + 5(n_{y,x}) + 6(n_{x,y})
\]

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Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

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 \( n=n_1=n_2=40 \), that

\[
f^+_x = 23; f^+_y = 22 \text{ and } f^+_z = 22; \text{ so that } \hat{\pi}^+_x = P_x = 0.575 (= a); \hat{\pi}^+_y = P_y = 0.550 (= b); \text{ and } \hat{\pi}^+_z = P_z = 0.550 (= c).
\]

From Table 3 we have that

\[
n_{y,x} = 12; n_{z,x} = 18, \text{ and } n_{z,y} = 16.
\]

Also

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

Hence

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

Finally from Table 4 we have that

\[
n_{z,xy} = 6 \text{ and } f^+_{z,xy} = 4.
\]

Hence

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

Note also from Table 4 that

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

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

<table>
<thead>
<tr>
<th>S/No</th>
<th>Event</th>
<th>Estimated Approval Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ABC</td>
<td>0.127</td>
</tr>
<tr>
<td>2</td>
<td>ABC</td>
<td>0.064</td>
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<td>3</td>
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<td>5</td>
<td>ABC</td>
<td>0.251</td>
</tr>
<tr>
<td>6</td>
<td>ABC</td>
<td>0.108</td>
</tr>
<tr>
<td>7</td>
<td>ABC</td>
<td>0.021</td>
</tr>
<tr>
<td>8</td>
<td>ABC</td>
<td>0.079</td>
</tr>
<tr>
<td>9</td>
<td>S_0(at least two evaluation committee)</td>
<td>0.635</td>
</tr>
<tr>
<td>10</td>
<td>S_0(evaluation committee and at least one other)</td>
<td>0.384</td>
</tr>
<tr>
<td>11</td>
<td>S_0(evaluation committee and at least one other)</td>
<td>0.442</td>
</tr>
<tr>
<td>12</td>
<td>S_0(evaluation committee and at least one other)</td>
<td>0.571</td>
</tr>
</tbody>
</table>

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...
Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

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

\[(0.575)(0.333) + (0.575)(0.556) + (0.530)(0.688) - 3(0.127) = 0.889 = 0.381 = 0.508,
\]

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 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**

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

Awad Magbri, MD, FACP & Thanh G Nguyen, MD

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 ultrastructural 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.

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 rhabdomyolysis and myoglobinuria. 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
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, Mikhalbкова 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


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
Childhood Hypocalcemia: The Aetiological Pattern

Nasir A. M. Al Jurayyan, MD

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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 hypoparathyroidism, 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.

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 laboratory, 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 hypoparathyroidism 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.7,8

Damage to the parathyroid glands is a well-established risk of neck surgery, especially during total or subtotal thyroidectomy. Permanent parathyroid...
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 irradiation. 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. 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%) patients in our series were diagnosed to have celiac disease.

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 Aljurayyan for her help and support.

Conflict of Interest

The author have no conflict of interest to declare.

REFERENCES Références Referencias

Table 1: Aetiology of childhood hypocalcemia in 60 patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>(%)</th>
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</thead>
<tbody>
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<td>Parathyroid hormone (PTH) deficiency (45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Isolated hypoparathyroidism</td>
<td>10</td>
<td>16.67</td>
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<tr>
<td>• Hypoparathyroidism associated with Sanjad-Sakatisyndrome</td>
<td>6</td>
<td>10.00</td>
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<tr>
<td>• Hypoparathyroidism associated with autoimmune polyendocrine syndrome</td>
<td>7</td>
<td>11.67</td>
</tr>
<tr>
<td>• Post-thyroidectomy</td>
<td>2</td>
<td>3.33</td>
</tr>
<tr>
<td>• Hypomagnesium</td>
<td>2</td>
<td>3.33</td>
</tr>
<tr>
<td>Rickets (41.7%)</td>
<td></td>
<td></td>
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<tr>
<td>• Nutritional rickets</td>
<td>13</td>
<td>21.67</td>
</tr>
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<td>• Anti-convulsant induced rickets</td>
<td>4</td>
<td>6.67</td>
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<tr>
<td>• Vitamin D dependent rickets Type 2</td>
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<td>• Hypophosphotemic Rickets</td>
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<td>3.33</td>
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<tr>
<td>• Pseudo hypo-hypo-parathyroidism type 1b</td>
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<td>1.67</td>
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<tr>
<td>Miscellaneous (13.3%)</td>
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<td></td>
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<tr>
<td>• Celiac disease</td>
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<td>• Chronic renal failure</td>
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<td>3.33</td>
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<tr>
<td>TOTAL</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>
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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:
Erlotinib Induced Fatal Interstitial Lung Disease: An Underreported Toxicity

Ramy Sedhom a, Elan Gorshein a, Jane Date Hon b, Judith Amorosa c, & Serena Wong y

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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). 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. The signaling pathway of EGFR is estimating to be activated in more than half of patients with NSCLC, increasing the role of targeted therapy. 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. 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. However, growing incidence of major adverse side effects, such as interstitial lung disease (ILD), continues to be reported since drug approval. 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 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
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 <44mmHg, 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 4). 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 acute organized 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.9 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. 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 is 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.

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.
Fibrin thrombi are seen within the vessels. There is acute inflammation, squamous metaplasia, and type 2 pneumocytes proliferate to replace the damaged alveolar cells. 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.

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 over the area of the radiation portal. Whether these exacerbates pre-erlotinib itself contributes to lung toxicity due to its own early after administration of chemotherapy. Whether this may be a predisposition to ILD.

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 lungs was also reported as a predisposition to ILD. 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, mitomycin, vinorelbine tartrate, docetaxel, ifosfamide. 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 exacerbates pre-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 erlotinib. 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.


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.
**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.
**Erlotinib Induced Fatal Interstitial Lung Disease: An Underreported Toxicity**

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, pCO₂ 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.
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

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

Dr. Richard Lee Pollock

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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 (GLV), including cruciferous vegetables (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...
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 OR 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
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 three different studies. Figure 2 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 HR effect size of the ‘almost every day’ highest vs. lowest quantile intake category of GLV on incidence of urothelial cancer as: 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.

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 adjustments 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
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: $\text{OR} = 0.749$ (95% CI 0.678 to 0.827), $p=0.001$, 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 RR 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: $\text{RR} = 0.803$ (95% CI 0.799 to 0.922), $p=.002$, 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 OR as their effect size. However, these three studies included 195,872 participants with 1,134 cases with 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: $\text{OR} = 0.896$ (95% CI 0.861 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%.

\textbf{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 carcinogenesis (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]).

\textbf{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.

\textbf{References Références Referencias}


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


15. Park S, Oliberding 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


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

<table>
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<th>Study</th>
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<th>Location</th>
<th>Effect Size</th>
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**Figure 1:** Forest plot showing a significant 25.1% lower risk of incidence from urothelial cancer by consuming a high quantile intake of GLV.

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

**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.
**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.
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.
Waldenstrom’s Macroglobulinemia Presenting as Syncope

By Ramy Sedhom, Daniel Sedhom, Angela Samaan & Syed Haqqie

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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 Macroglobulinemia (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 Macroglobulinemia associated syncope.

GJMR-F Classification: NLMC Code: WB182

Strictly as per the compliance and regulations of:
Waldenstrom’s Macroglobulinemia Presenting as Syncope

Ramy Sedhom a, Daniel Sedhom a, Angela Samaan p & Syed Haqqie o

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, hallmarkled 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 Macroglobulinema 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. Neurolgically 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 Macroglobulinema 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.

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

**III. Discussion of Differential Diagnosis**

Orthostatic 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/albunin 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**

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

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: A 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 third 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.

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 parapinealgloma, 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 CO₂ was maintained between 32-38mmHg. During the surgical procedure, the
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, PaCO₂ 33mmHg, HCO₃⁻ 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 140-150/70-80. 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, PaCO₂ 39.1 mmHg, HCO₃⁻ 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 tachypneic 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, HCO₃⁻ 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 PaCO₂ 13.2 mmHg, HCO₃⁻ 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, PaCO₂ 16.6mmHg, HCO₃⁻ 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°C. 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, PaCO₂ 26.6 mmHg, HCO₃⁻ 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, PaCO₂ 32.2 mmHg, HCO₃⁻ 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
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 from 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+, Ca2+, and Mg2+ 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 advertent 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


**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

<table>
<thead>
<tr>
<th>Time</th>
<th>pH</th>
<th>PaCO₂ (mmHg)</th>
<th>HCO₃⁻ (mmol/L)</th>
<th>B.E (mmol/L)</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 min into surgery</td>
<td>7.40</td>
<td>32.9</td>
<td>20.6</td>
<td>-3.7</td>
<td>0.4</td>
</tr>
<tr>
<td>4 hours into surgery</td>
<td>7.31</td>
<td>39.1</td>
<td>19.9</td>
<td>-7.0</td>
<td>1.5</td>
</tr>
<tr>
<td>1 hour post-surgery</td>
<td>7.43</td>
<td>13.0</td>
<td>9.1</td>
<td>-13.6</td>
<td>4.3</td>
</tr>
<tr>
<td>2 hours post-surgery</td>
<td>7.38</td>
<td>13.6</td>
<td>8.1</td>
<td>-15.4</td>
<td>4.9</td>
</tr>
<tr>
<td>6 hours post surgery</td>
<td>7.51</td>
<td>16.6</td>
<td>13.5</td>
<td>-8.4</td>
<td>1.4</td>
</tr>
<tr>
<td>8 hours post surgery</td>
<td>7.46</td>
<td>26.6</td>
<td>21.1</td>
<td>-4.0</td>
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</tr>
<tr>
<td>16 hours post surgery</td>
<td>7.42</td>
<td>32.6</td>
<td>22</td>
<td>-2.7</td>
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CENTRAL NEUROGENIC HYPERVENTILATION WITH ACUTE RESPIRATORY ALKALOSIS, TRANSIENT LACTIC ACIDOSIS AND TACHYCARDIA FOLLOWING ENDOSCOPIC THIRD VENTRICULOSTOMY IN A CHILD- A CASE REPORT

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Describe the Various Types of Neuropathy Observed in Patients with Diabetes

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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. 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. Approximately, 8% of general population suffer from long standing pain are caused by the neuropathic pain. Around 50% of chronic diabetics’ individuals (more than 25 years) will develop neuropathy which affect their daily living. 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%.

GJMR-F Classification: NLMC Code: WQ 248
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I. Introduction

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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. Warning sign of nerve impairment may comprise:

- 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

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.

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. Numerous theories of pathogenesis have been distinguished in the aetiology of DN such as:

- 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.

Theories concerning the numerous aetiologies of diabetic neuropathy comprise:

- 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. Neuropathic pain mechanisms can be summarized in following table:

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### Peripheral 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 mechanisms
- 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:
- 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:

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
   - Pathobiology

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.

There are four categories of diabetic neuropathy:

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

Essential Differential Diagnoses includes: Medicines (such as cytostatic drugs), Toxins, metals (such as 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:

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. 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.
Describe the Various Types of Neuropathy Observed in Patients with Diabetes


19. Smith AG, Singleton JR. Diabetic neuropathy. Continuum. 2012; 18: 60–84. This is an excellent and detailed review of DN.


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 hardware 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

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Staphylococcus Associated Glomerulonephritis with IgA Mesangial Deposition

Awad Magbri

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

1. **Case**

The case is that of a 52-year-old Caucasian male with a history of motor vehicle accident, status post open reduction and internal fixation of the left hip. He sustained a 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 hardware 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 removed. He was readmitted to the hospital with increasing pain and persistent drainage from the wound. Imaging was 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 hyperlipidemia. His medication consisted of insulin, lisinopril, iron, folate 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 otherwise 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.

2. **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 subepithelium 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-
morbidity 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%, leukocyturia 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 SAGN 2/11 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>49-50 years</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>Alcoholism +/- cirrhosis</td>
<td>2-57%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8-29%</td>
</tr>
<tr>
<td>COPD</td>
<td>7-33%</td>
</tr>
<tr>
<td>IVDU</td>
<td>3-27%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5-10%</td>
</tr>
</tbody>
</table>
Presentation
• Nephritic syndrome
• Nephrotic syndrome
• Mean serum creatinine
• Mean 24 hr protein
Kidney biopsy
• Endocapillary proliferation
• Crescents (>20-30%)
• Interstitial infiltration
• ATN
IF staining:
• C3 deposits
• C1q
• IgG deposits
• IgM/IgA
EM
• Mesangial deposits
• Sub-endothelial
• Humps
Sites of infection and microbiology
• URI
• SSTI
• Lungs
• Endocarditis
• Dental
• UTI
Organisms
• Streptococcus
• Staphylococcus
• Gram negative
• No growth

Table-2: differential from IgA nephropathy

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

References Références Referencias

6. Montoliu J, Miro JM, Campistol JM, et al. Henoch-Schonlein purpura complicating Staphylococcal...
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Complete support for both authors and co-author is provided.

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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-refered;

(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.

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**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.

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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 $1.4 \times 10^{-3}$ m$^3$, or 4 mm somewhat than $4 \times 10^{-3}$ 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.

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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.

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One should avoid outdated words.

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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.

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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.

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- Fundamental goal
- To the point depiction of the research
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- Significant conclusions or questions that track from the research(es)

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- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
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- Report the method (not particulars of each process that engaged the same methodology)
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- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

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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.

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- 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.

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- 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.
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