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The Results of Hearing Screening at the Children with Down Syndrome in Andijan Region of Uzbekistan

By Zebo Khakimjanovna Karimova

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Abstract- This article presents the primary results of targeted hearing screening among children with Down syndrome, as one of the most common pathologies at risk of developing various forms of hearing loss. As a result of the screening according to the data of delayed otoacoustic emission and otoacoustic emission distortion product, out of the total number of children in 41.5% of cases, objective tests showed the presence of auditory dysfunction, i.e. the answer is “refer”. Thus, we found it expedient to carry out hearing screening in children with Down syndrome in order to prevent hearing loss, and secondary forms of delayed psychoverbal development associated with it.

Keywords: *down syndrome, auditory screening, hearing loss, children with down syndrome, objective methods of audiometry.*

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The Results of Hearing Screening at the Children with Down Syndrome in Andijan Region of Uzbekistan

Zebo Khakimjanovna Karimova

Abstract- This article presents the primary results of targeted hearing screening among children with Down syndrome, as one of the most common pathologies at risk of developing various forms of hearing loss. As a result of the screening according to the data of delayed otoacoustic emission and otoacoustic emission distortion product, out of the total number of children in 41.5% of cases, objective tests showed the presence of auditory dysfunction, i.e. the answer is "refer". Thus, we found it expedient to carry out hearing screening in children with Down syndrome in order to prevent hearing loss, and secondary forms of delayed psychoverbal development associated with it.

Keywords: down syndrome, auditory screening, hearing loss, children with down syndrome, objective methods of audiometry.

I. INTRODUCTION

According to the European Down Syndrome Association (EDSA), 80% of people with Down syndrome of various ages have some form of hearing impairment, however, there are also cases of sensorineural hearing loss. Epidemiological studies show that the prevalence of moderate to profound hearing loss in children, including sensorineural hearing loss and conductive hearing loss, is up to 6:1000, with 10% of children having profound hearing loss [1].

Children with Down syndrome are at higher risk of hearing loss than their normally developing peers. According to the literature, 1.4 per 1000 newborns and 5 per 1000 children aged 3 to 7 years have hearing loss (Centers for Disease Control and Prevention, National Center for Birth and Developmental Defects, Division of Birth Defects and Developmental Disabilities 2013).

According to numerous studies, up to 20% of children may have sensorineural hearing loss caused by defects in the development of the inner ear and auditory nerve. They have narrow nasal passages, a small mouth, and tongue deviation. However, conductive hearing loss is observed in up to 70-78% of children with Down syndrome. The pathogenesis of conductive hearing loss is based on the anatomy and physiology of the maxillofacial skeleton, nasopharynx. Thus, the horizontal location of the Eustachian tube in combination

with muscular hypotension that occurs in diabetes causes frequent diseases of the middle ear, in particular exudative otitis media (EOM).

Modern pediatric audiology today allows for an objective assessment of hearing from the first days of a child's birth [2, 3, 4]. Such objective audiological tests as short-latency evoked auditory potentials (SAEP), delayed otoacoustic emission (DOAE), MultiASSR allow to obtain hearing thresholds in children regardless of age and psychological state. An important factor is the age aspect. It is well known that the so-called "second signaling system" is active in children under 3 years of age, and by the age of 5 it weakens in its physiological significance [5, 6, 7]. The preschool age of the child is therefore considered to be the most relevant and vulnerable in terms of hearing and further associated speech development, both for children from the general group and even more so for children with Down syndrome. Thanks to objective audiometry tests, hearing diagnosis in this age group of children has become possible, even in the presence of concomitant neuropsychiatric diseases [8, 9].

Thus, early diagnosis of hearing impairment in children with Down syndrome will allow not only adequate treatment and correction in a timely manner, but also to prevent STDs associated with auditory dysfunction, which in turn will guarantee an improvement in the quality of life of children with this pathology. However, the type and degree of hearing loss remain unexplored. Moreover, pathological changes in the central parts of the auditory analyzer in children with Down syndrome have not been studied and studied, which is reflected in the impairment of speech intelligibility with the preserved and normal functioning of its peripheral parts.

Thus, the fact of early diagnosis of hearing in children with Down syndrome is socially and economically justified, determining the timely correction, the effectiveness of subsequent rehabilitation in order to prevent secondary forms of delayed psychoverbal development in this group of children.

II. MATERIALS AND METHODS

The examination included 50 children with confirmed Down's syndrome, registered in the

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neurological dispensary, as well as in the departments of neurology of the Andijan regional multidisciplinary children's center and at the department of neurology of the clinic of the Andijan State Medical Institute. At the same time, the age of the children was t: 0-1 year 5 children (3 boys and 2 girls), 1-3 years 24 children (12 boys and 12 girls), 3-5 years 8 children (5 boys and 3 girls), 5-7 years 7 children (4 boys and 3 girls), 7-10 years 3 children (2 boys and 1 girl), 10< years 3 children (1 boy and 1 girl). The genetic analysis performed confirmed: 47 children had trisomy in 21 pairs (94%), 2 children had a mosaic form (4%), 1 child had a translocation form, 27 boys and 23 girls (2%). At the first stage, auditory screening was carried out using DOAE based on the Otoread clinical screening audiometer (Interacoustics) In this case, broadband acoustic clicks presented with a repetition rate of 20-50/s served as stimuli. DOAE registration criteria: the ratio of the emission power to the background noise power in three or more frequency bands, which was at least 3 dB. After reaching the required signal-to-noise ratio, the computer automatically stopped the work, issuing the "PASS" indicator - "test passed", if there was no answer after 1000 repetitions, the "REFER" indicator appeared - the test was not passed.

At the second stage, children with the result "failed" underwent complex objective audiometry under natural sleep - SAEP both in air and bone conduction, stationary evoked potentials - Multi-ASSR, game audiometry, and also acoustic impedancemetry. In-the-ear telephones with pre-fitted ear tips served as the source of sound stimuli. Cup silver chloride electrodes were used to record brain responses. The electrodes were fixed on the nasal region (ground electrode), on the border of the scalp (reference electrode) and in the region of the mastoid processes on the right and left (active electrodes). In the studies, the interelectrode resistance did not exceed 5 k Ω , which was achieved by preliminary treatment of the patient's skin and the use of special conductive gels. Various types of stimuli were used during the ABR, including an acoustic click with a duration of 100 ms, tone signals with a frequency of 1000, 4000, 2000 and 500 Hz, a broadband Chirp stimulus, and octave-filtered (frequency specific) Chirp stimuli. For analysis, it is recommended to record at least 2 runs (graphs) for each intensity value (to avoid false interpretation of artifacts).

III. RESULTS AND DISCUSSION

Out of 50 children with Down syndrome, DOAE showed the result of "refer", i.e. the response "failed" was registered in 24 children, which indicated the presence of auditory dysfunction in comparison with the control group. The absence of registration of DOAE at the same time on both sides was observed in 11 children (32.3%), and unilateral in 13 children (67.6%).

Accordingly, these 24 children with Down syndrome were subsequently referred for a comprehensive hearing diagnosis using objective audiological tests.

Behavioral (playing) tone audiometry was performed only in adult children older than five years and with convincing evidence of the adequacy of their response to the examination, providing reliable results only in 8 children (21.6%).

Impedance tests are quite informative, but their use has been limited by the high incidence of stenosis of the external auditory canal. The analysis of the obtained tympanograms was carried out according to the international Jerger classification. According to the data of the conducted tympanometry at 226 Hz, type "A" tympanogram, i.e. as normal, were obtained in 28 ears (28%). Type "B" was identified in 16 ears (16%), and type "As" was registered in the remaining 4 ears (%).

Tympanometry data at 1000 Hz in the same group of patients revealed type "B" in 23 ears (23%), type "A" in 15 ears (15%) and type As in 10 ears (10%). Stapedial reflexes were often absent even in the presence of type A tympanogram. This fact can be explained by severe weakness (hypofunction) of the tubal muscles.

Data on SAEP (CHIRP) detection of the V peak at a level above 30dB was shown in 11 ears (11%), 45-50dB in 28 ears (28%), making up the majority, in 2 ears (in one child with Down syndrome) was determined at the level 90-95 dB, which corresponded to bilateral sensorineural deafness. In the remaining 9 ears (9%), normal hearing threshold values were determined.

However, a comparative analysis of the SAEP data and the conducted tympanometric data showed greater information content and comparability when performing 1000 Hz typometry. Thus, according to our research and the data of foreign researchers on this issue, it is 1000 Hz tympanometry that is the most diagnostically reliable and valuable in this group of patients. Namely, it is necessary to take into account the features of the anatomy and physiology of the nasopharynx, the structure and pathology of the middle ear, as well as the maxillofacial skeleton in children with Down syndrome. The authors describe hypotheses: a narrow external auditory canal and an immature cartilaginous structure of the auricle reduce the level of sound transmitted to the tympanic membrane and middle ear system. Different types of fabrics show specific levels of resistance to each frequency, resulting in different levels of sound transmission. In addition, the sound compliance is determined by the mass of the structures of the middle ear and the effect of the rigidity of the skeletal system. The mass of the tympanic membrane, bone components (hammer, anvil, stirrup) determine mass reactions. The flexibility of the tympanic membrane, the bony transmission mechanism, and the tension of the perilymphatic fluid on the footrest of the stirrup determine the stiffness element. When

considering the anatomical and physiological conditions, the adult middle ear is defined as a system with adjustable stiffness at low frequencies, while the infant middle ear system is a mass-dominated system and requires more pressure. In the case of children with Down syndrome, this mechanism is more persistent and has almost the status of a constant in all age groups: a specific horizontal location of the Eustachian tube, prolonged presence of mesenchymal tissue in the tympanic cavity, stenosis of the external auditory canal, hypoplasia of the mastoid process, nasal passages, small mouth, language deviation.

IV. CONCLUSION

Thus, according to the data obtained, the following can be done:

1. In children with Down syndrome, complex objective hearing diagnostics can reveal even latent (minimal hearing impairments), which requires further audiological monitoring;
2. The incidence, type, and degree of auditory dysfunction is often unrelated to the genetic type of Down syndrome;
3. The most common form of hearing loss in children with Down syndrome is conductive hearing loss (39%), which is determined by objective tests and confirmed by tympanometry at 1000 Hz;
4. Taking into account the anatomical and physiological features of the structure of the ENT organs in children with Down syndrome, tympanometry at 1000 Hz shows greater information content and sensitivity than at 226 Hz.

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Molecular Detection of Human Papillomavirus using Flow Chip Methodology

By Beatriz Valbão Pires, Fabrício Antônio Ferreira Martins,
Elisângela Flávia Pimentel & Schmitt, Denise Coutinho Endringer

Universidade Vila Velha

Abstract- Human papillomavirus (HPV) infection is the most common sexually transmitted disease globally, affecting mainly women and being responsible for developing oral and cervical cancer. This study aims to determine the presence of HPV and its high and low-risk subtypes in women who submitted to the HPV genotyping test. One hundred thirteen vaginal secretion samples were collected from August 2018 to August 2019 from women aged between 17 to 78 years. The material was analyzed for HPV genotyping using a Flow chip methodology, 39 samples were identified positive for the HPV virus, while 74 samples did not present the virus. No relation between HPV infection and age could be established. Considering the groups, it was possible to identify two peaks of infection, one occurring in the class between 16 to 25 years and another in between 46 – 55. This result was not expected since the second class's age is not considered a high risk for HPV.

Keywords: HPV, cervical cancer, flow chip, molecular biology.

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MOLECULAR DETECTION OF HUMAN PAPILLOMAVIRUS USING FLOWCHIP METHODOLOGY

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Molecular Detection of Human Papillomavirus using Flow Chip Methodology

Beatriz Valbão Pires ^α, Fabrício Antônio Ferreira Martins ^σ, Elisângela Flávia Pimentel ^ρ
& Schmitt, Denise Coutinho Endringer ^ω

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Keywords: HPV, cervical cancer, flow chip, molecular biology.

1. INTRODUCTION

Sexually Transmitted Diseases (STD) refers to a group of infections and syndromes caused by pathogens, which can be transmitted or acquired through sexual activity (Workowski and Bolan, 2015). STDs represent one of the biggest health problems globally, especially in developing countries (Agaçdan and Kohl, 2006). In Brazil, some factors make it difficult to control this group of diseases, such as the scarcity of epidemiological data and high incidence associated with self-medication, causes the patients not to be informed and treated, favoring their dissemination (Araújo and Silveira, 2007). These infections can be divided into two groups, curable and non-curable, the latter being exemplified by Human Immunodeficiency Virus (HIV), Herpes virus, Hepatitis B, and Human Papillomavirus (HPV), all caused by viruses (Agaçdan & Kohl, 2006). HPV is the most common STD globally (Foldvari, 2011), being the most common to affect women (Burchell et al., 2006). According to the World Health Organization (WHO),

about 291 million women are infected with HPV globally (World Health Organization, 2018). Its transmission occurs through contact with the skin or mucous of infected individuals. However, its transmission does not necessarily occur by a fluid exchange. It can be transmitted via oral sex, manual-genital contact, or even to the baby by the mother during birth (Vento and PROADI-SUS, 2017). HPV is a non-cultivable, non-enveloped DNA virus (Ministério da saúde. Secretaria de vigilância em saúde, 2010) belonging to the Family Papillomaviridae (Rosa et al., 2016), and to the genus Papillomavirus (de Lima Camara et al., 2003).

To date, approximately 250 types of Papillomavirus (Eça, 2004), its structure has a double DNA, with about 8000 base pairs (Nakagawa et al. 2010) (Paavonen, 2007), that is divided into three parts, L, E, and LCR. The genes found in the L (late) region are responsible for the formation of proteins that form the viral capsid. In the E (early) region, the genes are responsible for producing proteins involved in the malignancy of the host cell and proteins responsible for controlling the replication of the virus's DNA. The LCR (Late Control Region) is where promoters of these genes are located and the origin of DNA replication (Eça, 2004).

L1 is an important region, very conserved in all types of HPV, this region of the virus is used for genotyping (Nakagawa et al., 2010; Paavonen, 2007). The HPV subtypes differ in at least 10% in the nucleotide sequence of the L1 region (de Lima Camara et al., 2003). The types responsible for genital tract infection are divided into two groups. These groups are separated according to their low and high-risk oncogenic potential. The first group is related to benign infection of the genital tract (Ministério da saúde. Secretaria de vigilância em saúde, 2010). Those in the second group are highly related to carcinomas (Herraez Hernandez et al., 2013), causing subclinical lesions that can progress to cancer (World Health Organization, 2018). These cervical lesions are known as cervical intraepithelial neoplasia (CIN). These neoplasms may be grade I, which only indicates the presence of the virus, or grade II and III, which are already precursor lesions of cervical cancer (Cohen et al., 2019). Therefore, the HPV the etiologic agent is a major contributor to the development of benign

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neoplasms such as laryngeal papillomatosis (Martins et al., 2008) and malignant neoplasms such as oral and cervical cancer (Araújo et al., 2014 ;Nakagawa et al., 2010). The word cancer is a name for a set of 100 malignant neoplasms, having in common disorderly cell growth (Wild, 2014). Cervical cancer was one of the most common cancers affecting women worldwide (Bray et al., 2018) and the second most common type of cancer to hit women in Latin America (Wild, 2014) with high mortality in developing countries, second only to breast cancer (Bray et al., 2018). In 2018, 16,370 new cases of cervical cancer were estimated in Brazil, according to the National Cancer Institute - INCA. The most important thing for the success of the treatment is the discovery of the lesions in the early stages (Silva, 2019). With previous and periodic exams, it is possible to identify symptomatic and asymptomatic patients, thus controlling the spread of HPV (Bezerra et al., 2005).

The most common manifestations of HPV are genital warts. In these cases, the most common subtypes are 6 and 11 (Borsatto et al., 2011). 70% of cervical cancer cases worldwide are associated with subtypes 16 and 18 (World Health Organization, 2008). Subtype 16 was the most common subtype in cases of cervical cancer in Brazilian regions (Rosa et al., 2009). The vaccine is the most suitable method to prevent infection, and currently, there are two types of prophylactic vaccines, intending to combat the spread of HPV and the lesions caused by the virus, the bivalent (subtypes 16 and 18), and the tetravalent (subtypes 6, 11, 16 and 18). These vaccines are indicated for women between 9 and 26 years (Silva et al., 2009).

Currently, HPV diagnosis is made using molecular biology tests. If lesions are identified during the prevention examination, a biopsy should be performed to distinguish benign from malignant (Brasil, 2010). Among the methodologies utilized for HPV diagnosis, the Flow Chip methodology stands out as it's a fast and sensitive molecular test for HPV detection and genotyping. DNA extraction is unnecessary when the samples are crude cells, such as cervical swabs, paraffin tissue, or liquid cytology (Herraez-Hernandez et al., 2013).

Therefore, this study aimed to determine the presence of the human papillomavirus and its high and low-risk subtypes in women who took the exam of genotyping HPV employing the Flow chip methodology, with the hypothesis that the presence of HPV is age-related in the patients, so that the highest occurrence of the virus is in the age group of 16 to 25 years, in which sexual activity begins.

II. METHODS

a) Sample collection

The samples of cervical-vaginal secretion were collected during the preventive exam, using liquid-based

cytology from August 2018 to August 2019. The patients who took the exam of genotyping HPV at Cremasco Medicina Diagnóstico, are residents of the cities of Vila Velha, Vitória, Cariacica, Viana, Guarapari, Serra and Domingos Martins. The samples are stored refrigerated (2 to 8 ° C) until the analysis, which was carried out at the Cremasco Medicina Diagnóstica.

b) Sample preparation

After the cells were seated on the bottom of the vessel, 200 µl of the suspension was removed and transferred to a 1.5 ml Eppendorf. The sample was then centrifuged at 2000 rpm for 3 minutes. The cell suspension was removed, leaving only an accumulation of cells (pellet) in the microtube. That pellet was resuspended in 400 µl of PBS 1X and again centrifuged at 2000 rpm for 3 minutes. The suspension was removed, leaving only about 30 µl of that. The polymerase chain reaction (PCR) was carried out with 4 µl of the suspension and an additional 36 µl of a mixture of HPV Primers, Enzyme DNA polymerase Hot Start and Enzyme Uracil DNA Glicolase. PCR is an in vitro technique formed by cycles typically consisting of 3 stages, denaturation, annealing and extension, amplifying DNA exponentially, generating billions of copies of a target sequence (Pereira, 2018). The target region for amplification is the L1 region during the PCR reaction. The reaction is formed by 53 cycles, the first at 25 °C for 10 min, the second at 94 °C for 3 min, and then a set of 15 cycles. 94 °C for 30 s, 42 °C for 30 s, 72 °C for 30 s, followed by 35 cycles of 94 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s, followed by a 72 °C cycle for 5 min (Herraez-Hernandez et al., 2013).

c) Flow Chip HPV detection

The Mobius® Multiplex HPV Kit was used for the qualitative detection and genotyping of 36 different types of Human Papilloma Virus, these being 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82 high oncogenic risk and the subtypes 6, 11, 40, 42, 43, 44, 54, 55, 61, 62, 67, 69, 70, 71, 72, 81, 84, and 89, low risk (Figure 1). The HPV flow chip protocol is based on the amplification of the HPV target region (PCR) and the application of these denatured products on the membranes of individual chips that contain probes for controls and universal HPV infection and the specific detection of 36 genotypes. After the reaction, the PCR product undergoes a denaturation of 95 °C for 10 minutes in the thermal cycler. After the denaturation, the reverse hybridization process begins. Its specific DNA probes are immobilized on a chip composed of a nylon membrane. The PCR product binds to the probes present on the chip, and a colourimetric reaction generates the hybridization signal. This reaction produces a purple precipitate in the position that corresponds to the amplified fragment of PCR hybridized with the specific probe. This signal is read

and analyzed by software connected to the equipment (Herraez-Hernandez et al., 2013).

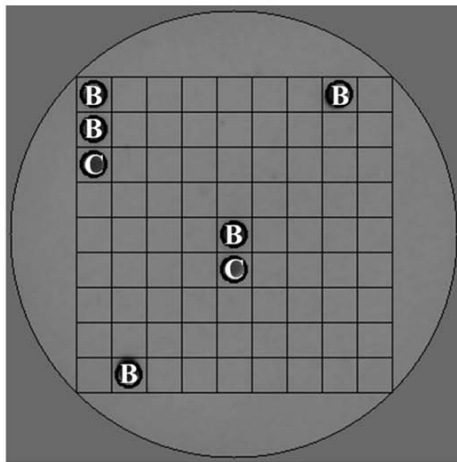


Figure 1: This image shows a negative result and the controls to monitor. B: hybridization control indicates that the hybridization process worked correctly. C: endogenous amplification control (β -globin) indicates that the amplification worked correctly, and the clinical sample contains human DNA.

d) Statistical analysis

The samples were separated according to the patient's age, which generated six age groups. These classes were based on the risk class for STD infections which is 16 to 25 (Vento and PROADI-SUS, 2017). The classes are 16-25, 26-35, 36-45, 46-55, 56-65 and > 66 . A G test was performed on all classes using the BioEstat 5.3 program. The expected number of sick patients for each class was calculated based on the proportionality of sick patients within the sample. In addition, prevalence by class was calculated.

III. RESULTS

One hundred thirteen samples were analyzed, and 39 samples (26,5%) presented the HPV virus was distributed in high and low-risk subtypes (Table I), while 74 were not detected. The subtypes and their degree of risk of progressing to cancer were also identified among the positive samples. Patients with more than one HPV subtype (8) were identified, presenting low-risk and high-risk subtypes. The prevalence detected in this study was 34.5%.

Table 1: Total samples (n=113) with and without detection of HPV, subtypes and risk degree

Results	N	Risk Degree	Subtype
Not detectable	74	-	-
Detectable	39		
	3	Undefined	*Genotype not identified
	14	Low risk	6, 11, 42, 43, 44, 54, 62 and 81, 84
	14	High risk	31, 33, 35, 51, 56, 58, 73
	8	Both	6, 31, 39, 42, 43, 44, 45, 51, 55, 62 and 81, 73

*Subtype not detected by the Mobius® HPV Multiplex Kit.

The origin of the patients who underwent the examination was predominant in Cariacica (n = 55), followed by Vila Velha (n = 24). Other cities were Vitória (n = 8), Serra (n = 8), Domingos Martins (n = 5), Viana (n = 4), Guarapari (n = 1) and seven patients did not provide their address. The median age of HPV positive patients are 29. 25 to 75% of the patients are between 23 and 46 years old. For negative patients, the median was 36.5, and 25 to 75% of patients were between 32 and 48 years old. According to the test result - G (Williams), there was no significant difference between classes. However, with the patient index (D) divided by the total N of class (N) (Table II), it was possible to observe two peaks of infection, one occurring in class 16 - 25 and the other in class 46 - 55, being exactly in classes where the observed value was higher than the expected value.

IV. DISCUSSION

The prevalence of the current study was 34.5%, a similar result found by Holanda Jr et al. (2006) in Ceará, with a prevalence equal to 33.9% and lower than that found by Carestiato et al. (2010) in Rio de Janeiro, with a prevalence of 54, 3%. In the study by Araújo et al. (2014) in Belém, the prevalence was 24.1%, and de Sanjosé et al. (2007) identified a prevalence of 12.3% in South America. To better understand the occurrence of HPV in the population, women were divided into classes according to their age, and it was possible to observe that there was no association between infection and the patient's age. Araújo et al (2014) also found no association for both variables. However, through meta analyses, de Sanjosé et al. (2007) observed that the infection is more common in women under 25 years old. It is still unclear how age can influence the prevalence of HPV, but several studies show that the prevalence is higher in women under 25, with a decrease after that age (De Sanjosé et al., 2007; Matos et al., 2003). Adolescents are a the population of high vulnerability to sexually transmitted diseases as sexual intercourse begins, as they do not always use methods to prevent these diseases (34). The prevalence of HPV appears to have a bimodal behavior. It is possible to identify two peaks in the sample. The first in class is 16 - 25 years old and the second in class, 46 - 55 years old. De Sanjosé et al. (2007) observed the same behavior, who found an estimate of the prevalence of Higher HPV in women under 34. In the next group, there was a drop, and it increased again in the group of 45 - 55 years old. This behavior was observed in women from almost all regions of the world. Giuliano et al. (2005) found the same situation on the border between Mexico and the United States of America. In Brazil, this behavior was observed by Pinto et al. (2011) in Eastern Amazon and by Rama et al. (2008) in the cities of Campinas and São Paulo. The HPV subtypes found in this study were 6, 11,

31, 33, 35, 39, 42, 43, 44, 45, 51, 54, 55, 56, 62, 73, 81, and 84, of which eight subtypes are considered high risk and 9 low- risk (Herraez-Hernandez et al., 2013). The HPV tetravalent vaccine prevents the subtypes most associated with cervical cancer and genital warts.

In addition to identifying the virus in the sample, the genotyping carried out in this study is significant, allowing us to know whether HPV is the oncogenic type. When there is the persistence of an infection with a specific subtype of high-risk HPV, it can be decisive for the development of cervical neoplasms, interfering in the treatment of lesions. More intense approaches are indicated for treating infections caused by high-risk subtypes than low-risk ones (Burd, 2003). In most cases, the body can get HPV, but there are exceptions. With weakened immunity, the body cannot eliminate the virus (Ministério da saúde. Secretaria de vigilância em saúde, 2010).

With the diagnosis of CIN I, the most indicated treatment is periodic exams to monitor the progression of the lesion, as only 11% of CIN I progress to CIN II or III. In the case of those progressing to high-grade injuries, a more intense the approach is needed than in the case of CIN I, and the most common is to perform an excision of the transformation zone (Derchain et al., 2005). One of the main cause of cervical cancer are persistent HPV infection, which is also associated with prolonged use of oral contraceptives, immunosuppression, and smoking. 6.385 deaths due to cervical cancer were registered in Brazil in 2017 (Silva, 2019). The treatment of precursor lesions is of great importance to reduce the incidence and mortality from cervical cancer (Burd, 2003).

V. CONCLUSION

In conclusion, it was possible to determine the presence of human Papillomavirus in the analyzed samples, in which both high and low-risk groups were found. No association was found between the patient's age and the presence of HPV, so it is impossible to relate the patient's age to the infection, but this result may be related to the sample size. A study with a larger sample size would be necessary to investigate these variables more effectively.

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Healthy Lifestyles in Patients with Type 2 Diabetes Mellitus and Alteration Genetic Compatible with Ctp-Ii According to Clinical Evidence

By Estefany Rivera-Moreno & Milton Manuel Rivera- Moreno

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Introduction- Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. According to the International Diabetes Federation (IDF) [1]

Carnitine palmitoyltransferase (CPT) catalyzes the transfer of long- and medium-chain fatty acids from cytoplasm into mitochondria, where oxidation of fatty acids takes place. Deficiency of CPT enzyme is associated with rare diseases of fatty acid metabolism. CPT is present in two subforms: CPT I at the outer mitochondrial membrane and carnitine palmitoyltransferase II (CPT II) inside the mitochondria. Deficiency of CPT II results in the most common inherited disorder of long-chain fatty acid oxidation affecting skeletal muscle. [2]

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Healthy Lifestyles in Patients with Type 2 Diabetes Mellitus and Alteration Genetic Compatible with Ctp-Ii According to Clinical Evidence

Estilos De Vida Saludables En Pacientes Con Diabetes Mellitus Tipo 2 Y Alteración Genética Compatible Con Ctp-Ii Según Evidencia Clínica

Estefany Rivera-Moreno ^α & Milton Manuel Rivera- Moreno ^ο

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. According to the International Diabetes Federation (IDF) [1]

Carnitine palmitoyltransferase (CPT) catalyzes the transfer of long- and medium-chain fatty acids from cytoplasm into mitochondria, where oxidation of fatty acids takes place. Deficiency of CPT enzyme is associated with rare diseases of fatty acid metabolism. CPT is present in two subforms: CPT I at the outer mitochondrial membrane and carnitine palmitoyltransferase II (CPT II) inside the mitochondria. Deficiency of CPT II results in the most common inherited disorder of long-chain fatty acid oxidation affecting skeletal muscle. [2]

Obesity and type 2 diabetes are caused by a combination of poor diet quality, high caloric intake, and physical inactivity. The skeletal muscle accounts for 50% of total energy expenditure (EE), and because it is highly bioenergetically demanding and insulinresponsive, it greatly affects systemic metabolism in physiological and pathological scenario [3].

Carnitine palmitoyltransferase II (CPT II) deficiency is an important cause of recurrent rhabdomyolysis in children and adults. Current treatment includes dietary fat restriction, with increased carbohydrate intake and exercise restriction to avoid muscle pain and rhabdomyolysis [4]. The term "fats" designates a set of nutrients with great chemical heterogeneity, due to their different composition in fatty acids. Therefore, it is totally logical consider that its biological effect will vary depending on the type of fatty acid predominant in its molecule. All fats are insoluble in water and soluble in organic solvents, they are present in all cells (animal and plant) and most can be synthesized from carbohydrates [5].

According to Khazrai and collaborators, there are many food plans available so that patients with DM2 can choose one based on their personal tastes and cultural traditions. It is important to provide a personalized diet when possible in order to increase its effectiveness in reducing diabetes symptoms and encouraging patient adhesion [6].

There is currently no specific etiological treatment. General recommendations include avoiding situations that can precipitate myoglobinuria, such as intense exercise, and a diet high in complex carbohydrates and low in fat can be useful to ensure glucose supply from liver glycogen stores [7].

A concise review of the available clinical evidence on this topic is carried out, where we can conclude that having multiple comorbidities leads to adjusting changes in healthy lifestyles, in this case of metabolic pathologies, the clinical evidence is clear about the advantages and good quality of life that is obtained by having an adequate adherence not only in the pharmacological treatment but also by a suitable diet, which must be individualized and given by a trained multidisciplinary team that allows reaching the goals and in turn avoiding complications.

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

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.



Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- 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.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
- k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

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



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

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

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

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning 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 a research paper?" Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.



Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

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Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

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

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

TIPS FOR WRITING A GOOD QUALITY MEDICAL RESEARCH PAPER

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

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

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

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

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

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10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

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

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

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

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

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

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.



20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

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

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

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

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

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The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

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

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

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- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

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

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

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

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- To-the-point depiction of the research.
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Approach:

- Single section and succinct.
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- Concentrate on shortening results—limit background information to a verdict or two.
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Approach:

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Approach:

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- Recommendations for detailed papers will offer supplementary suggestions.

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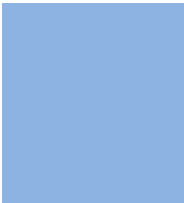


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<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring





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