KAYSERI CHILD HEALTH ASSOCIATION

JP

The Journal of PEDIATRIC ACADEMY

Year 2024

Volume 5 | Issue 2

e-ISSN: 2718-0875

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Journal Name	Journal Short Name	Publishing Language	Broadcast Period	ISSN/E-ISSN
The Journal of Pediatric Academy	J. Pediatr. Acad. (JPA)	English	4	2718-0875

Starting Date	Publication Type	Indexed	Journal Concessions
2020	Periodicals (Online)	TUBITAK ULAKBIM TR Dizin EBSCO Türk Medline DOAJ Google Scholar EuroPub Asos Indeks J-Gate	Kayseri Child Health Association

Journal Management Location and Address

The Journal of Pediatric Academy Office,
Kayseri Chamber of Medicine,
Seyitgazi Mah. Nuh Naci Yazgan Cad. Geriatri Merkezi Binası K:1 N:4, Melikgazi, Kayseri - Türkiye
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Research Articles:

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Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1.
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Manuscript Type	Word Limit	Abstract Word	Limit Reference	Limit Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	100	No abstract	5	1	1

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Example: Multiple studies have indicated….[1,3,9,16]

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Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tıp Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Publication Date: June 2024
E-ISSN: 2718-0875
International scientific journal published quarterly.

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Journal of Pediatric Academy

Invited Review

Year: 2024 Volume: 5 Issue: 2
Doi: 10.4274/jpea.2024.309
J Pediatr Acad 2024; 5: 37-43

Integrating Child Life Specialists in Pediatric Oncology and Hematology Care: A Narrative Review

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Article Information

Article Type: Invited Review
Article Group: Pediatric Oncology

Received: 26.04.2024
Accepted: 30.05.2024
Epub: 06.06.2024
Available Online: 01.07.2024

Cite this article as: *Abdelkhalik M, Ibrahim M, Al Maaz F, Boutros E. Integrating Child Life Specialists in Pediatric Oncology and Hematology Care: A Narrative Review. J Pediatr Acad. 2024; 5: 37-43*

Abstract

Many healthcare systems overlook the importance of enrolling a child life specialist (CLS) on board, possibly due to the lack of knowledge and awareness on the impact they might yield. This study highlights the essential contributions of CLS in improving pediatric oncology healthcare experiences. A thorough search of numerous databases was performed to identify English-language publications between 2005 and 2024, using a variety of study methods to establish a diverse evidence base. CLSs offer emotional support, educate patients and their families, implement distraction techniques, and collaborate with healthcare personnel to assist patients throughout their treatment journey. They also aid in providing adequate knowledge to patients and their families regarding medical procedures and treatment outcomes. Hence, CLSs play a vital role to play in the care of pediatric hematology oncology patients. A comprehensive interdisciplinary approach is needed to extend the role of CLS and ensure that every child receives the support and care they deserve.

Keywords: Child life specialist, pediatric oncology, pediatric hematology, pediatric cancer care

Introduction

In the field of pediatric healthcare, where anxiety and uncertainty are common, child life professionals prioritize the emotional well-being of children during these difficult moments. These trained healthcare professionals are specialized in offering emotional, developmental, and psychosocial support for children experiencing illness and advocating for the holistic care of young patients.[1]

The role of child life specialists (CLSs) extends beyond typical healthcare paradigms, embracing a wide range of interventions adapted to each child's individual needs. According to the American Academy of Pediatrics (AAP), CLS can provide expert advice and support in managing a child's pain.[2] Furthermore, CLS reduce the negative effects of treatments by promoting adaptive behavior and resilience. Overall, their role includes providing age-

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appropriate explanations of medical procedures, therapeutic play interventions, active coping strategies, education, play, and expressive activities.[3] By providing all the aforementioned services, CLS has a pivotal role in reducing stress and anxiety for children undergoing painful procedures.[4]

Cancer in children comprises only 2% of all cancer cases, yet it is the second most common cause of death in children older than 1 year after trauma.[5] CLS are vital assets in pediatric oncology, offering crucial assistance to children and families navigating the complex and emotionally difficult treatment journey. Families benefiting from the expertise of certified CLS have reported alleviation of fear, anxiety, and stress, among other positive outcomes. Hence, CLS can aid in reducing the impact of these challenging times on the child and his/her family and improving the overall quality of life.[6]

This study seeks to underscore the invaluable contributions of CLS in enhancing pediatric oncology healthcare experiences. We will shed light on how CLS promotes coping, resilience, and general well-being among pediatric patients and their families by analyzing their contributions in different settings and through different procedures. By highlighting their expertise, interventions, and effects, we aim to stimulate additional study, advocacy, and cooperation to ensure that every child receives the support and care they need during times of sickness or injury.

Methodology

Search Strategy and Inclusion Criteria

This original review was written in April 2024. The authors conducted a search using PubMed, Cinahl, Web of Science, Medline, and Science Direct using the following keywords: "Child Life Specialist", "Pediatric Oncology", and "Hematology".

The following inclusion criteria were used:

1. Articles published in English.

2. Articles published between 2005 and 2024 were deemed to reflect contemporary research and advancements.

3. The study included case-control, cross-sectional, cohort, and review papers to collect a broad variety of information on the subject.

Selection Process

The two authors conducted the literature searches separately, guaranteeing a thorough search of the given databases. Zotero automatically detects and removes duplicate articles. After deleting duplicates, the remaining items were screened on Rayyan. During the screening process, the authors separately assessed the titles and abstracts of these papers, removing any article that did not fulfill the inclusion criteria. The exclusion criteria at this stage included research unrelated to the topic, non-English papers, and those published before 2005.

The following title and abstract screening, the entire text of the submitted articles was examined to determine their suitability for inclusion in the research. The summary and visual depiction of selection process is presented in **Figure 1**.

Data Analysis

Two writers independently extracted data from the included studies. Data extraction included important information such as the function of the CLS, duties, constraints, primary results, and any other information relevant to the review's aims. This technique ensured that the literature was evaluated comprehensively and thoroughly. Following this methodological procedure, we tried to find and select papers that were most relevant to the review's aims, providing a solid framework for our research.

Results and Discussion

Understanding Pediatrics Oncology and Hematology

A child cancer diagnosis is a complex process involving multiple procedures and operations where children often experience anxiety and distress, mostly stemming from the treatment's challenges and not the cancer itself.[7] Patients and their parents often feel the urge to start the treatment as soon as the diagnosis has been confirmed, which negatively impacts their daily routine and causes further distress.[8] Studies have shown that pain and anxiety were reported by 50-60% of children with cancer when receiving various medical operations and nearly 63% developed a fear of healthcare professionals.[5]

In addition to anxiety and fear, pain is among the most prevalent unpleasant feelings experienced by children with cancer. Expressed by crying, twisting, and muscle stiffness,[9] pain is thought to contribute to anxiety and fear experienced by the child. These feelings are heightened during treatment, possibly because of exposure to unfamiliar environments and separation anxiety.[10]

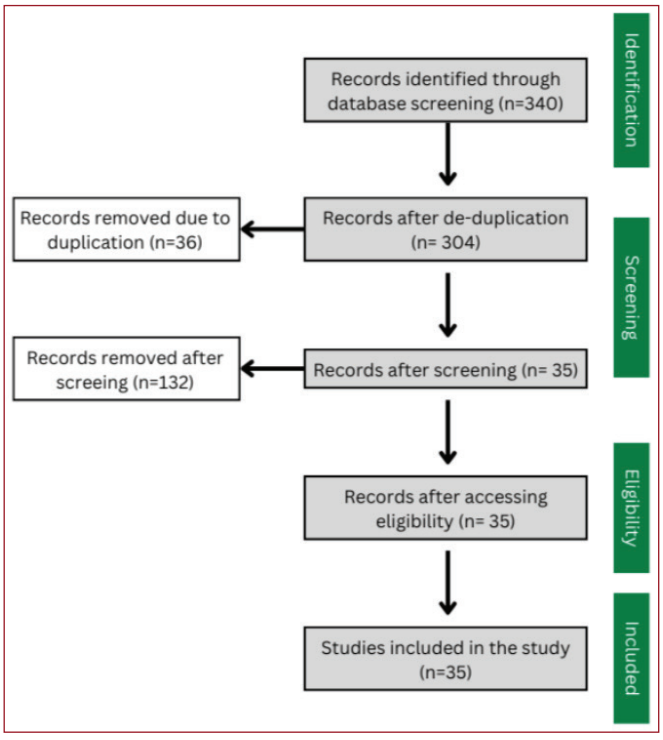

Figure 1. PRISMA flow diagram of literature screening for CLS and pediatric hematology/oncology

CLS: Child life specialist

The prospect of painful treatments, intrusive procedures, and probable side effects looms large, casting a shadow of fear over the treatment journey. Many children are terrified of numerous medical procedures, anxious about the uncertain progression of their disease, and worried that they are different from other children.[11] Surgical procedures can elicit various unfavorable emotions from children, with 50%-65% suffering from perioperative anxiety.[12]

Pediatric hematology and oncology encompass a wide spectrum of illnesses and therapies that require specialized care and attention owing to their complexity and possible influence on a child's well-being. Chemotherapy, radiation therapy, and stem cell transplantation are among the principal therapeutic techniques, each imposing considerable physical and emotional difficulties on pediatric patients. The side effects of these procedures, such as nausea, hair loss, fatigue, and immunosuppression, have a great impact on the child's quality of life and necessitate careful care provided by CLSs.[13-15] Other painful medical procedures that lead to anxiety in children include venipuncture, bone marrow, lumbar punctures, and placement of central venous catheters.[16] In addition, port needle operations are the most disturbing, frightening, and painful aspect of children's chemotherapy treatment.[11] Furthermore, the long-term complications and late effects experienced by childhood cancer survivors, including secondary malignancies, infertility, cardiotoxicity, and neurocognitive deficits, necessitate comprehensive follow-up and survivorship care.[17,18] Considering these complexities, a multidisciplinary approach encompassing the expertise of CLS is important to provide support and optimize outcomes in pediatric hematology and oncology. The main findings of the study are summarized in **Table 1**.

Highlights

- Child life specialists (CLSs) have played a crucial role in the mental and physical aspects of patients' well-being. Unfortunately, many healthcare systems overlook the importance of enrolling a CLS, possibly due to the lack of knowledge and awareness on the impact they might yield.
- The study conducted a thorough systematic search of various databases for English-language articles published between 2005 and 2024 discussing the use of virtual reality in pediatric oncology procedures.
- CLSs offer emotional support, educate patients and their families, implement distraction techniques, and collaborate with healthcare personnel to assist patients throughout their treatment journey. Challenges include insufficient knowledge and awareness of children's needs, lack of recognition of CLS' work, and lack of institutional support.

Role of the CLS

Definition and Historical Background

CLSs emerged in the mid-20th century (1920) as part of pediatric healthcare.[19] In the 1960s, CLS was founded as a medical specialty by Emma's efforts Plank.[20] Emma Plank, a pioneer in the field, emphasized the importance of play therapy and emotional support for hospitalized children. She proposed the idea of playrooms inside hospitals that would allow children to engage in activities.[21] In addition, by 1960, the AAP had published a study and guidelines for the treatment of children in hospitals, advising that all pediatric units include a playroom equipped with suitable items such as games, toys, and books.[3] The Child Life Council, which became known as the Association of Child Life Professionals in 2016, was founded in 1982 to promote child wellbeing while also providing professional support and development opportunities for CLS.[22] The council established criteria for education, training, and certification in the sector, thus promoting its professionalization and growth.[19] Since then, CLS has become a fundamental aspect of pediatric treatment, both inpatient and outpatient, and has achieved favorable results in several settings.[23]

Importance of Psychosocial Support in Pediatric Hematology and Oncology

Hospitalization can be a significant stressor for children, leading to several negative consequences if not managed properly.[24] Indeed, children may retain long-term memories of pain, potentially prolonging the recovery process.[25] Additionally, recurrent hospitalizations may affect cognitive, emotional, and social development.[26] This is where the importance of addressing these challenges reveals itself, as children who received child life services experienced reduced levels of anxiety compared with those who did not.[1] These results have an important impact because lower stress levels are linked to better healing outcomes for children. In addition, CLS has a positive impact on the psychological aspect of anxiolysis and improves the child's experience.[27]

Roles and Responsibilities of CLS

The existing research mainly addresses children's psychological needs in parallel with the role of CLS, focusing on emotional support, proper preparation for medical procedures, play therapy, distraction techniques, education, and advocacy.

Emotional Support for Patients and Families

CLS contributes to the establishment of a safe and supportive environment where children are encouraged to openly express their emotions and receive experience validation when needed. This is done in various ways, including active listening, acknowledgment of the child's emotions, reassurance, and encouragement. This continual emotional validation and support helps to normalize children's emotional responses to illness, hospitalization, and medical procedures.[28]

Child coping, behavioral cooperation, and levels of discomfort were all measured in a study assessing the impact of CLS intervention on the emotional

Table 1.
Showing the main findings of our study

Main findings	Author
50-60% of children diagnosed with cancer experience pain and anxiety when undergoing medical operations.	Miller et al.[5]
Venipuncture, bone marrow, lumbar punctures, and placement of central venous catheters are among the main medical procedures that lead to anxiety in children.	Loeffen et al.[16]
The assistance of child life services reduced the anxiety levels of children, which is linked to better healing outcomes and improvement in experience.	Murag et al.[27]
The reduction of moral distress and burnout among clinical personnel improving their mental health and well-being is also attributable to CLS.	Rosenblatt et al.[28]
A positive correlation between the impact of CLS intervention on the EMS of pediatric patients undergoing polysomnography was described.	Baughn et al.[29]
A significant reduction in healthcare costs is noticed due to a decrease in the need for daily sedation when CLS provides play-based procedural preparation and support for the children.	Grissom et al.[31]
Physical or technology-based distraction tools are important for improving patient satisfaction during cast room procedures.	Burkhart et al.[35]
Child life intervention plays an important role in alleviating the negative symptoms of pain, fatigue, and anxiety in patients with acute leukemia undergoing chemotherapy.	Li et al.[38]
Playing video games daily did not affect the performance of pediatric chemotherapy patients.	Hamari et al.[40]
Almost all physicians in U.S. pediatric urology agreed on the positive impact of CLS on their patients' quality of life.	Mistry et al.[41]

CLS; Child life specialists, EMS; Emotional manifestation score

manifestation score of pediatric patients undergoing polysomnography. Interestingly, a statistically significant positive correlation was observed for those who were offered CLS. Their results also suggest that CLS emotional support not only enhances children's coping mechanisms with medical procedures but also leads to higher satisfaction scores from patients and families.[29]

In parallel to the above, another study compared the experience of children with lacerations in the emergency room with and without CLS and found that CLS engagement was related to decreased emotional distress.[30] In fact, the emotion-focused supportive interventions performed by CLS have been very effective in enhancing resilience, upscaling coping skills, and mitigating traumatic experiences.[28]

Educational Preparation for Medical Procedures and Treatment

CLS plays an important role in introducing patients and their families to upcoming medical procedures using age-appropriate simplified language. They explain the procedure, establish expectations, and support all members using various techniques such as distraction and vocalization. To assist the child in processing the experience, CLS are also in charge of performing post-procedural debriefing.[29] Dolls are useful tools frequently used by CLS as they psychologically prepare their patients, especially pre-operatively.[31]

The role of CLS also extends into the procedure itself, where their presence and interventions reduce the duration of procedures while improving imaging quality in radiology departments.[32]

In addition to the procedure itself, CLS assists families in understanding their child's treatment response and maintaining their caregiving roles. This includes encouraging play sessions, introducing distraction techniques, and training them on emotionally supportive strategies for comforting their children during medical procedures. As for the siblings of young age groups, CLS helped them to comprehend the illness through age-appropriate lectures and repeated visits to the hospital.[33] Specially trained CLSs are also qualified to offer grief support activities for siblings in the setting of catastrophic injury or death or episodes of terrorism.[34]

Play Therapy and Distraction Techniques

Games, being familiar and reassuring to children, have aided in making the healthcare experience more comfortable and less intimidating.[33] Studies on play-based procedural preparation and support intervention provided by a CLS show a significant drop in healthcare costs because it reduces the necessity of daily sedation.[31]

In addition, other interventions, including therapeutic play and distraction techniques, are implemented to reduce fear, anxiety, and pain among pediatric patients and their families. A meta-analysis conducted by Burkhart et al.[35] described physical or technology-based distraction tools as key players in improving patient satisfaction during cast-room procedures. Most of the adopted tools were inexpensive and readily applicable to the clinical setting. Similarly, a cross-sectional study revealed that 45% of parents consider play intervention as one of the key factors in enhancing their experience during hospital stay. Only 5% of the parents had persistent reported stress about the illness after CLS intervention.[31]

Collaborating with Healthcare Teams

CLS cannot yield effective results if operated on its own. They are members of multidisciplinary teams that collaborate with physicians, nurses, social workers, and palliative care centers. CLS not only impacts patients and their families but also has a positive impact on the mental health and well-being of clinical practitioners through their constant support to reduce moral distress and burnout.[28]

Impact and Benefits

Effectiveness of CLS in Pediatric Hematology and Oncology

Here, we may begin by mentioning a case study by Basak et al.[36] that describes the role of CLS in the treatment journey of a 14-year-old boy known to have progressive ependymoma with hydrocephalus and multiple secondary metastases with impending herniation of the brain. The patient was depressed, anxious, and uncooperative with the staff. After several failed attempts by the CLS provider, he noticed that the patient had a special interest in magic. As a result, a medical student, dressed like a magician, helped the patient interact, smile, and relax. The parents and the patient reported feeling more emotionally supported after this initiative.[36] Such a case reveals the importance of adapting one's approach to tailor to the needs and interests of each individual child.

In another retrospective study conducted on sickle cell disease pediatric patients, results showed that a patient's encounter with CLS can enhance health care experience through support and education, especially during the transition process from a pediatric hematology patient to an adult hematology patient.[37]

Similarly, Li et al.[38] assessed the effect of CLS interventions on acute leukemia patients undergoing chemotherapy. Their results show that child life intervention can effectively lessen pain, control anxiety, decrease fatigue, and limit sleep disturbances. Music therapy also appears to help lower anxiety and fear in pediatric oncology patients performing a lumbar puncture.[39]

In contrast, a randomized control trial conducted by Hamari et al.[40] showed no significant difference in terms of physical activity, motor performance, and fatigue in chemotherapy pediatric participants when asked to play video games daily. Although this study does not include CLS, play therapy and distraction techniques do not seem to make a significant difference in the treatment of pediatric oncology patients.

Unfortunately, the current literature lacks sufficient cross-sectional studies on CLS effectiveness specifically targeting the pediatric hematology oncology population.

Patient and Family Perspectives on the Role of CLS

Since CLS is not globally implemented in the healthcare system, examining the knowledge and perspectives of patients and parents on CLS becomes crucial. On the one hand, almost all physicians felt that CLS did benefit their patients' quality of life in a study conducted in the U.S. in pediatric urology.[41] Another study assessing parents' satisfaction and perception of inpatient CLS showed that most parents did not know about CLS before their first admission but were satisfied with the interventions they received on the floor.[42] This shows the need to properly communicate the role of CLS to all parents, possibly during their outpatient visits to their pediatricians, or through informative workshops and training.

Challenges and Future Directions

Challenges Faced by CLSs in Pediatric Hematology and Oncology

Taneja et al.[43] conducted a review of CLSs' experiences in adult oncology settings and highlighted a range of challenges that hinder practitioners from fully implementing their expertise in the children's plan of care. These challenges coexist in adult and pediatric settings and stem from the inherent nature of the work. Insufficient knowledge and awareness of children's needs in such settings and the lack of recognition of CLSs' work often leads to delayed involvement. Furthermore, many of these cases are morally challenging, leading practitioners to struggle to do what they think is best for the child. In addition, the families' wishes to withhold information about the diagnosis from their children add an additional layer of complexity to the responsibilities of CLSs and can potentially lead to resentment and trust issues from the child. Other limitations worthy of consideration include the inconsistency of follow-up frequently encountered (especially post-mortem), minimal involvement of the specialist by the primary care physician, and the overall lack of institutional support.[43]

Opportunities for Further Research and Development in This Area

CLS integration in every pediatric oncology patient's plan of care requires a transformative approach starting at the medical school level. Comprehensive interdisciplinary education programs should underscore the importance of CLS involvement and endorse teamwork, communication, and collaboration skills to meet patients' needs.[44] At the operational level, early involvement of CLSs is vital for establishing trust and rapport with the child and the family.[45] This can be encouraged by an opt-out, rather than opt-in, hospital system. In addition, it is essential that the primary care team educates the patient's family on the holistic nature of child well-being and stresses the family-centered approach for treatment.[46] In this regard, Brosnan et al.[47] also highlighted the importance of implementing sibling assessment and support in the plan of care. An intricate evaluation and quality improvement system that continuously monitors and assesses CLS in oncologic floors and disseminates data should also be established.

Overall, advocacy and awareness campaigns on the unique contributions of CLSs in pediatric oncology care among healthcare professionals and the wider community are essential in promoting policies and supporting CLS integration in the plan of care.

Conclusion

CLS play an important role in pediatric hematology and oncology by providing critical assistance to children and their families as they deal with the emotional challenges of illness. Their expertise in meeting the particular requirements of children with cancer and blood disorders ensures that care goes beyond medical treatment, encouraging resilience and assisting them in overcoming obstacles. As we look ahead, possibilities for research, development, and comprehensive multidisciplinary

education programs hold promise for expanding the role of CLS, especially in the field of pediatric oncology, and ensuring that every child receives the support and care they need.

Acknowledgments

We would like to thank Joseph El Haddad, who contributed to this project by reviewing the manuscript and making the necessary English language edits.

Informed Consent: The consent form was not needed due to the study design.

Author Contributions: Mohamad Abdelkhalik: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Maria Ibrahim: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Fatima Al Maaz: Literature Search, Writing.; Eliannore Boutros: Writing.

Conflict of Interest: The authors revealed no possible conflicts of interest with regard to the research, authorship, and/or publication of this work.

Financial Disclosure: The authors declared that this study received no financial support.

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Journal of Pediatric Academy

Original Article

Year: 2024 Volume: 5 Issue: 2
Doi: 10.4274/jpea.2024.292
J Pediatr Acad 2024; 5: 44-49

Assessment of Oxidative Stress and Plasma Gelsolin Levels in Children with IgA Vasculitis

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Article Information

Article Type: Original Article
Article Group: Pediatric Rheumatology

Received: 14.02.2024
Accepted: 04.05.2024
Epub: 21.05.2024
Available Online: 01.07.2024

Cite this article as: *Danacı B, Baştuğ F, Karakükcü Ç, Çelik B, Çeleğen K. Assessment of Oxidative Stress and Plasma Gelsolin Levels in Children with IgA Vasculitis. J Pediatr Acad. 2024; 5: 44-49*

Abstract

Oxidative stress has been proposed to contribute to the pathogenesis of immunoglobulin A vasculitis (IgAV), but the available data remain insufficient. Our goal was to determine the role of the oxidant-antioxidant system and plasma gelsolin (pGSN) in patients with IgAV and its relationship with organ involvement. In the study, 30 individuals with IgAV diagnoses and 30 healthy controls were enrolled. All patients were examined in both the active and remission periods. Serum malondialdehyde (MDA), superoxide dismutase (SOD), and pGSN levels were measured. Compared with the remission and control groups, active IgAV patients had higher serum MDA levels; however, this difference was not statistically significant. When comparing the acute period to remission and control, serum SOD levels were somewhat lower; however, the difference was not statistically significant (>0.05). pGSN levels were prominently low in IgAV patients both in the acute and remission phases (<0.05). No correlation was found between organ involvement, serum MDA, antioxidant enzyme (SOD), and pGSN levels. Low pGSN levels in patients with IgAV may be due to pGSN consumption during the acute episode of the inflammatory process. This may tilt the delicate equilibrium between oxidants and antioxidants, potentially amplifying reactive oxygen species generation.

Keywords: IgA vasculitis, children, oxidative stress, plasma gelsolin

Introduction

Immunoglobulin A vasculitis (IgAV) is the most common vasculitis involving small vessels in childhood, and more than 90% of patients are under the age of 10 years.[1,2] IgAV can affect many tissues and organ systems, including the skin, joints, gastrointestinal system (GIS), and kidneys.[3] Although the exact cause of IgAV activation remains unknown, various substances, including nourishment, medications, antigens, pathogenic agents, and immunizations, have been linked to IgAV activation.[4] The prognosis is determined on the extent of kidney involvement, and the disease is typically self-limiting.[5]

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IgA is the predominant immunoglobulin of mucosal immunity. A multi-hit hypothesis has been proposed for the pathogenesis of IgAV. Immune complexes containing galactose-deficient IgA play a central role in the pathogenesis of IgAV. Because of their large size, immune complexes containing IgA may escape hepatic degradation and accumulate in the circulation and subsequently in tissues.[6] This stimulates a widespread pro-inflammatory cascade including neutrophil activation, complement, cytokine, and chemokine secretion, the release of neutrophil extracellular traps, and increased levels reactive oxygen species (ROS). This process is believed to lead to endothelial damage and IgAV development.[6]

Oxidative stress and increased ROS production are considered one of the core mechanisms of endothelial cell injury in IgAV.[6,7] Previous studies focusing on oxidative stress in the pathogenesis of IgAV have shown elevated concentrations of malondialdehyde (MDA) in tissues, blood, and body fluids, which is used as an indicator of oxidative systems due to lipid peroxidation.[8,9] ROS also inhibits nitric oxide production in endothelial cells, damages endothelial cell DNA, and leads to apoptosis.[6] Plasma gelsolin (pGSN), which is an important actin-binding protein and regulator of cellular skeleton dynamics, has been reported to possess antioxidant and anti-apoptotic properties.[10] In inflammatory conditions such as rheumatoid arthritis, trauma, and sepsis, a decrease in pGSN levels has been observed, but its relationship with pathogenesis and therapeutic role remains unclear.[11]

Oxidative stress may contribute to the disease, but it is unclear whether it is a cause or result of the disease course.[12] Oxidative stress can also occur when antioxidant mechanisms are out of balance. There have been contradictory findings from earlier research on the contribution of oxidative stress to the pathophysiology of IgAV regarding the overall antioxidant state.[12,13] In this study, we aimed to evaluate the levels of oxidative and antioxidant enzymes, as well as pGSN, in the active and remission periods of patients with IgAV to determine their contributions to the pathogenesis of the disease. Our aim also encompassed evaluating the connection between these markers and disease activity and organ involvement.

Material and Method

Patient Selection and Demographics

This prospective case-control study was conducted on individuals diagnosed with IgAV between May 2014 and August 2015 at our hospital's pediatric nephrology unit. Patients aged 2-16 years who were diagnosed with IgAV according to the College of Rheumatology (ACR) and the European League Against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) were included in the study.[14] Individuals were considered eligible for inclusion if they had laboratory samples available from each of the active and remission periods of the disease. Patients with chronic disease, active infection, ongoing treatment, and using nonsteroidal anti-inflammatory drugs or steroids before admission were excluded. Before enrollment in the study, informed consent was obtained from the families of all participating children. The study was approved by the Ethics Committee of our institution (date: 02.06.2017, no: 2017/296 - Erciyes University Clinical Research Ethics Committee).

Patients with IgAV diagnosis were evaluated in both active and remission periods, and laboratory samples were obtained. IgAV-active was defined as the assessment at the time the disease was first diagnosed, and IgAV-remission was defined as the 6-8 week period after the disease diagnosis. Demographics (age, sex, the presence of chronic disease, drug use, infections), and organ involvement were recorded. Following the patient selection process, a control group of healthy children who were selected from the pediatric outpatient clinic and matched the patient group in terms of average age and sex was formed. Complete blood count parameters, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), kidney and liver function tests, urine microscopy, and urine protein-creatinine ratio were studied in all patients.

Detection of Serum MDA, SOD, and pGSN Levels

Serum MDA, serum superoxide dismutase (SOD) activity, and pGSN levels were studied to assess oxidative stress in patients with IgAV and the control group for comparison. Venous blood samples (5 mL in volume) were collected from all IgAV patients before treatment. Blood samples were centrifuged, and the supernatant was stored at 800 °C.

Serum MDA levels were measured using the MDA kit (Cayman Chemical), which provides a simple, repeatable, and standardized tool for testing lipid peroxidation in plasma, serum, urine, tissue homogenates, and cell lysates. The color change formed by the reaction of MDA and thiobarbituric acid under high-temperature (90-100 °C) and acidic conditions was measured colorimetrically via a spectrophotometer at 530-540 nm. Serum SOD activity was measured using the micro ELISA method (Cayman Chemical). Using this method, total SOD activity (cytosolic and mitochondrial) was measured. pGSN levels were measured using a quantitative sandwich enzyme immunoassay method, performed using an ELISA kit (Biomatic, pGSN USA). The plate was precoated with an antibody specific to human gelsolin. The antibody could be bound to human gelsolin in the standard and samples. After washing the unbound substances in the coating, a biotinylated antibody against human gelsolin is added to the wells. In the second wash, streptavidin-horseradish peroxidase (HRP) conjugate was added. After the last wash, to remove unbound enzyme, a substrate solution (3,3',5,5'-Tetramethylbenzidine, TMB) is added to the wells, and color develops in standard solutions or in proportion to the amount of human gelsolin bound in the sample. Color development was stopped, and the intensity of the color was measured at 450 nm. Despite the logarithms of the gelsolin concentrations, the data were linearized by showing the optical density logarithms in point form. The pGSN concentration in the samples was calculated using the slope line formula.

Statistical Analysis

The analysis was performed using the Statistical Package for the Social Sciences, version 22.0 for Windows (IBM Corp., Armonk, NY, USA). QQ plots and a Shapiro-Wilk test were used to analyze the normal distribution of parametric data. For discrepancies between the IgAV-active and IgAV-remission parameters, a dependent sample t-test (paired sample t-test) was used. The patient and control groups were compared using an independent sample t-test, and the findings are presented as mean ± standard deviation. Variance homogeneity was examined using the Levene test. Correlations between parameters were evaluated using either the Pearson or Spearman coefficient. A p-value 0.05 was considered statistically significant.

Highlights

- Increased generation of reactive oxygen species and consequential oxidative stress are recognized as fundamental mechanisms underlying endothelial cell injury in immunoglobulin A vasculitis (IgAV).
- Plasma gelsolin (pGSN) is a protein known for its antioxidant and anti-apoptotic properties, which was found to be prominently low in both the active and remission phases of IgAV.
- The reduced amount of pGSN in patients with IgAV may be attributed to its consumption during the acute episode of the inflammatory process.

Results

The IgAV group included 19 boys (63%) and 11 (37%) girls, and the control group included 12 boys (40%) and 18 girls (60%) (p=0.07). No significant difference was noted in the mean age between the patient and control cohorts (9.21±4 vs. 8±3.8; p=0.25). At the first admission, all IgAV patients had palpable purpura, 25 of the patients (83.3%) had articular purpura, 17 (56.6%) had gastrointestinal purpura, three patients had kidney (10%) and scrotal involvement (10%). One patient developed scalp edema. Of all patients with joint involvement, nonsteroidal anti-inflammatory medications (n=15; 50%) were used in their treatment. Steroid treatment was administered to 15 (50%) patients with scalp edema, scrotal edema, GIS involvement, and renal involvement. In follow-up, remission was achieved in all patients in an average of 6-8 weeks, but one of the patients with GIS and kidney involvement went into remission after approximately 5 months with high-dose steroid treatment.

Table 1 displays the biochemical analyses of the subjects. The mean leukocyte number, platelet count, and CRP levels were significantly higher in the IgAV-active group than in the IgAV-remission and control group (<0.05). ESR levels in the IgAV active and remission groups were much greater than those in the control group <0.05. In comparison with the control group, the IgAV-active and remission groups had significantly decreased serum albumin levels (<0.05).

Oxidative biomarker levels of the groups are demonstrated in **Table 2**. Children with active IgAV had greater MDA levels than those in the remission and control groups, although this difference was not statistically significant. No correlation was observed between ESR, CRP levels, and MDA levels. SOD levels were slightly lower in the acute phase compared with those in remission and control, but it was not significantly different (>0.05). In comparison to the control group, the IgAV-active and -remission groups had significantly reduced pGSN levels. (Median pGSN IgAV-active vs IgAV-remission; p=0.021, IgAV-active vs. control p=0.003, IgAV-remission vs. control p=0.006). There was no relationship between age and sex and pGSN levels (>0.05). There was no correlation between inflammatory markers and pGSN levels (ESR; r=0.206, p=0.36, CRP; r=-0.09, p=0.68). As shown in **Table 3**, no significant relationship was found between organ involvement, serum MDA, SOD, and pGSN levels.

Discussion

Understanding the pathogenesis of IgAV is essential for the development of appropriate therapies. The pathogenesis of IgAV has been the subject of many theories. However, none have been clarified. The pathophysiology of IgAV is also believed to involve oxidative damage and lipid peroxidation. In this study, lipid peroxidation, an antioxidant enzyme, and pGSN levels in patients diagnosed with IgAV were investigated. pGSN levels in IgAV patients were observed to be considerably lower than those in controls, particularly during the acute phase.

Oxidant molecules produced by various reactions are neutralized by natural antioxidant molecules that are always present at certain levels in the body.[13] Oxidative stress is the disruption of the existing balance that releases free radicals and ROS, resulting in the activation of inflammatory cells and endothelial damage. Elevated levels of ROS can exert direct cytotoxic effects and impact mitochondrial respiration, thereby inducing lipid peroxidation in the cell membrane.[6] MDA arising from membrane lipid peroxidation is considered indicative of the extent of endothelial cell damage. In previous studies, elevated serum MDA levels were demonstrated in the acute phase of IgAV.[13,15,16] Zhu et al.[17] demonstrated a positive correlation between serum MDA levels and the degree of pathological grade in IgAV nephritis patients. Their findings suggest that the intensity of the inflammatory response and oxidative stress are closely related to the seriousness of the disease in IgAV.[17] In the current study, higher serum MDA levels were found in patients with IgAV in the active and remission phases compared with controls, but the difference was not significant. In addition, no correlation was observed between MDA levels and organ involvement. In agreement with our results, Kisaoglu et al.[12] found no difference in serum MDA levels between acute and remission phases in patients with IgAV. In both of these latter studies, no association between lipid peroxidation and IgAV activity and organ involvement was demonstrated, but this may be because the participants had mild diseases.

The following damage to vascular endothelial cells, neutrophils are stimulated and produce huge amounts

Table 1.
Comparison of laboratory parameters of the IgAV-active, IgAV-remission, and control groups

Variables	IgAV-active n=30	IgAV-remission n=30	Control n=30	IgAV-active vs. IgAV-remission	IgAV-active vs. control	IgAV-remission vs. control
				p*	p#	p#
HGB (g/dL)	13.2±1.5	13.5±1.3	12.8±0.7	0.33	0.19	0.02
MCV (fL)	82.1±5.1	82.2±5.4	81.2±5.1	0.77	0.52	0.48
WBC (/mm^3)	9763.7±2729	7821.7±3806	7016.7±2599	**0.006**	**<0.001**	0.09
PLT (x10^3/mm^3)	379±88	338±90	334±52	**0.003**	**0.02**	0.84
MPV (fL)	8.83±0.93	8.92±0.97	9.81±0.6	0.34	0.93	0,60
ESR (mm/h)	13.43±9.96	8.06±7.95	4.13±3.83	**0.007**	**<0.001**	**0.02**
CRP (mg/L)	22.16±22.64	5.62±6.79	3.45±0.75	**<0.001**	**<0.001**	0.09
Protein (g/dL)	6.76±0.67	6.74±0.52	7.16±0.45	0.83	**0.01**	**0.001**
Albumin (g/dL)	3.87±0.49	4.26±0.33	4.5±0.34	**<0.001**	**<0.001**	**0.009**

Statistically significant results (p<0.05) are shown in bold
*: Data were analyzed using the paired t-test.
#: Data were analyzed using an independent sample t-test
IgAV; Immunoglobulin A vasculitis, HGB; Hemoglobin, MCV; Mean corpuscular volume, WBC; White blood cell count, PLT; Platelet count, MPV; Mean corpuscular volume, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate

Table 2.
Comparison of oxidative stress biomarkers between the IgAV-active, IgAV-remission, and control groups

Variables	IgAV-active n=30	IgAV-remission n=30	Control n=30	IgAV-active vs. IgAV-remission	IgAV-active vs. control	IgAV-remission vs. control
				p*	p#	p#
MDA (µmol/L)	11.408±3.254	10.138±2.367	10.030±2.467	0.10	0.07	0.86
SOD (U/mL)	4.9±2.3	4.7±1.9	5.2±2.3	0.35	0.67	0.35
pGSN (µg/mL)*	104.5±72.1	74.8±50.97	265.1±257.4	**0.021**	**0.003**	**0.006**

Statistically significant results (p<0.05) are shown in bold
*24 patients
*: Data were analyzed using the paired t-test
#: Data were analyzed using an independent sample t-test
IgAV; Immunoglobulin A vasculitis, MDA; Malondialdehyde, SOD; Superoxide dismutase, pGSN; Plasma gelsolin

Table 3.
Comparison of serum MDA, SOD, and pGSN levels according to joint involvement, GIS involvement, and renal involvement

		Joint involvement			GIS involvement			Renal involvement		
Variables	**Involvement**	**n**	**Mean ± SD**	**p**	**n**	**Mean ± SD**	**p**	**n**	**Mean ± SD**	**p**
MDA	Yes No	25 5	11.09±3.07 12.98±4.03	0.24	17 13	10.97±3.07 11.97±3.51	0.41	3 27	10.16±3.2 11.54±3.28	0.49
SOD	Yes No	25 5	4.83±2.23 5.52±2.63	0.54	17 13	4.92±2.4 4.96±2.18	0.96	3 27	4.02±0.68 5.04±2.36	0.47
pGSN	Yes No	21 3	99.8±75.2 137.1±35.4	0.41	14 10	106.8±47.9 101.3±87.1	0.85	3 21	82.1±75.5 107.7±72.9	0.57

MDA; Malondialdehyde, SOD; Superoxide dismutase, pGSN; Plasma gelsolin, GIS; Gastrointestinal system, SD; Standard deviation

of ROS that further favor the progression of IgAV. The maintenance of a dynamic balance between the generation and removal of ROS depends on the antioxidant enzyme systems.[8] In comparison with healthy controls, Zhu et al.[17] found that patients with IgAV had significantly decreased levels of antioxidant enzymes (SOD and total antioxidant capacity) throughout the acute phase. They discovered that individuals with organ involvement and IgAV with nephritis had considerably decreased antioxidant enzyme activity.[17] Consistent with our research findings, Demircin et al.[15] demonstrated that serum SOD levels were slightly lower in the acute phase than in the remission phase, but this difference was not statistically significant. In addition, another study reported significantly lower levels of SOD and glutathione peroxidase in the early time of IgAV than in the remission phase. While a notable increase in the activities of antioxidant enzymes was noted during remission, their levels persisted below those observed in the control group.[16] Ece et al.[13] demonstrated a lower total antioxidant status and arylesterase activity in active patients compared with the control and remission phases. Furthermore, there were no appreciable variations between the active and remission phases of other antioxidant enzymes, such as catalase and paraoxonase; however, their levels were lower in the treated group than in the control group.[13] Compared with remission and control, SOD levels were lower in the active phase but not statistically significant in our study. The small number of patients with nephritis in our study may be the reason for the difference between these enzyme levels.

Cytoplasmic gelsolin is an important component of cellular dynamics; it is an actin-regulating protein required for phagocytosis and cell motility, and it also has antibacterial and anti-inflammatory qualities.[18]

The extracellular gelsolin isoform is called pGSN, and its physiological relevance remains unknown. In infectious and inflammatory conditions, such as sepsis,[19] rheumatoid arthritis,[20] and multiple sclerosis,[21] pGSN levels are markedly low. Simultaneously, gelsolin-actin complexes have been observed in the synovial fluid of patients with rheumatoid arthritis.[22] In an IgA nephropathy model, Han et al.[18] reported lower pGSN levels in serum and increased deposition of GSN in mouse kidneys. This finding was validated in a human study where serum levels of IgA nephropathy patients were significantly lower than those of patients with other glomerular disorders and healthy controls.[23] They also showed an association between higher renal tissue GSN levels and mesangial proliferation and sclerosis according to the Oxford classification.[23] A later *in vitro* investigation revealed that GSN aided in cell mitosis, which in turn enhanced the proliferation of human mesangial cells.[23]

Of the available studies, only one investigated the role of pGSN in individuals with IgAV, revealing diminished pGSN levels during the active period of IgAV in comparison with those in healthy controls.[24] In the current study, pGSN levels were measured in patients with IgAV during both active and remission periods, and the results were compared with those of controls. The pGSN levels were also considerably low during the active and remission periods and were much more pronounced during the remission period. pGSN levels did not correlate with organ involvement in this study. This may be due to the use of pGSN in the acute phase of the inflammatory process and its continuation until the disease was in remission. There was no discernible association between the levels of pGSN and markers indicating active inflammation. On the other hand, a reduction in pGSN could lead to an imbalance between oxidative enzymes and an increase in ROS levels.[18] It's not clear whether the illness process is caused or impacted by pGSN levels.

Study Limitations

Our study has some limitations. Our study was conducted with a small patient population. Therefore, oxidant and antioxidant enzyme levels in patients with IgAV, which were found to be significantly different in previous studies, may not have differed from the control group in this research. Compared with earlier research, fewer individuals in our study had severe illness and nephritis. This may have limited our evaluation of the relationship between organ involvement and oxidative stress markers. Despite these limitations, we assessed patients in both active and remission phases and compared them with the enzyme levels in healthy individuals.

Conclusion

In summary, to the best of our knowledge, this is the first well-designed study comparing the levels of pGSN in patients with IgAV during both the early and remission stages. IgAV is a systemic inflammatory disease, and the role of oxidant and antioxidant systems is important in its pathogenesis. The diminished plasma levels of GSN observed in patients with IgAV suggest a contribution of this protein to the pathogenesis. To better understand the connection between oxidative stress, pGSN, and IgAV pathogenesis, further research is required.

Ethical Approval: The study was approved by the Ethics Committee of our institution (date: 02.06.2017, no: 2017/296 - Erciyes University Clinical Research Ethics Committee).

Informed Consent: Before enrollment in the study, informed consent was obtained from the families of all participating children.

Author Contributions: Danacı B: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Baştuğ F: Concept, Design, Data Collection or Processing, Literature Search, Writing. Karakükcü Ç: Surgical and Medical Practices, Writing.; Çelik B: Data Collection or Processing, Literature Search, Writing.; Çeleğen K: Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: Our study was funded by the Kayseri Education and Research Hospital Clinical Research Education Board.

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Journal of Pediatric Academy

Original Article

Year: 2024 Volume: 5 Issue: 2
Doi: 10.4274/jpea.2024.277
J Pediatr Acad 2024; 5: 50-55

Hyperthyroidism in Pediatric Patients in a University Hospital: Ten Years of Experience

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Article Information

Article Type: Original Articles
Article Group: Pediatric Endocrinology

Received: 05.12.2023
Accepted: 15.05.2024
Epub: 05.06.2024
Available Online: 01.07.2024

Cite this article as: *Kocabey Sütçü Z, Eklioğlu BS, Atabek ME. Hyperthyroidism in Pediatric Patients in a University Hospital: Ten Years of Experience. J Pediatr Acad. 2024; 5: 50-55*

Abstract

Although rare in childhood, hyperthyroidism is diagnosed by suppressed serum thyrotropin (TSH) levels and increased levels of free triiodothyronin (fT3) and free thyroxine (fT4) in addition to history and physical examination findings. In this study, we aimed to investigate the causes of hyperthyroidism and the clinical features of the disease in children and to evaluate the treatment. A total of 39 patients with hyperthyroidism diagnosed between 2010 and 2019 in the pediatric endocrinology department were included in the study. The diagnosis of hyperthyroidism was established on the basis of the suppressed serum TSH level and increased fT3 and/or fT4 levels with clinical findings. Thirty-one (79.5%) patients were female, and the mean age of admission was 14.4 (4.3-17.5) years. Of the cases, 33 (84.6%) were diagnosed with Graves' diseases and 6 (16.7%) with Hashimoto thyroiditis. The most frequent complaints of patients diagnosed with hyperthyroidism were irritability (24, 61.5%), palpitation (22, 56.9%), and sweating (21, 53.8%). The most frequent findings were goiter in 31 (79.5%) patients and tachycardia in 27 (69.2%) patients. Serum TSH levels were suppressed in all patients, fT3 levels were increased in 94.4% of them, and fT4 levels were increased in 80.5% of them. In patients with Graves' disease, TSH receptor antagonist was positive in 31 (93.9%) cases, and at least one of the thyroid autoantibodies was positive in all patients. Antithyroid drug treatment was initiated in all patients; 35 of them received methimazole and 4 of them received propylthiouracil. Radioactive iodine treatment was applied to three patients, and two patients were treated surgically who did not respond to antithyroid drug treatment. Antithyroid drug adverse effects were observed in 7 (21.2%) patients, requiring drug discontinuation in 1 patient. Although hyperthyroidism is rare in childhood, its treatment is difficult and requires close follow-up. Treatment options are different for adult patients. There is a need for multicenter studies to evaluate treatment efficacy and long-term outcomes in children.

Keywords: Hyperthyroidism, child, TSH, Graves' disease

Introduction

In childhood, hyperthyroidism is a rare thyroid gland disease caused by increased thyroid hormone levels. Increased synthesis and secretion of thyroid hormones results in increased metabolism. The most common cause is Graves' diseases in childhood.[1] Other reasons include; thyroiditis, toxic adenoma, hyperthyroidism due

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to iodine excess, thyroid hormone resistance, pituitary adenoma producing thyrotropin (TSH), and occasionally exogenous high-dose thyroid hormone intake.

The incidence of Graves' disease, the main cause of hyperthyroidism in children, is approximately 1/10.000 in this age group. Graves' disease is an immunogenetic disease characterized by diffuse goiter, hyperthyroidism, and infiltrative ophthalmopathy. It is more common in females and peak in the adolescent age group.[2] Anti-thyroid drugs, radioactive iodine (RAI) therapy, and surgery are treatment options for hyperthyroidism. The level of TSH receptor antagonist (TSHRAb) and the size of the thyroid tissue are often helpful in determining the efficacy of drug treatment.[1,3]

Here, we evaluated patients with hyperthyroidism who were followed up in the pediatric endocrine department of a university hospital.

Material and Method

Patient Selection

A total of 39 pediatric patients between 0 and 18 years of age who were followed up with a diagnosis of hyperthyroidism in the department of pediatric endocrinology between 2010 and 2019 were included in the study.

The age of admission, age at diagnosis of patients who were diagnosed in another center, gender, consanguinity, family history of thyroid disease, accompanying disease, medication use, admission complaints, clinical findings, thyroid hormone and thyroid autoantibody levels, treatment regimens, adverse effects, and treatment outcomes were retrospectively recorded from the patient files.

Body weight and height measurements of the patients at diagnosis were recorded. Body mass index (BMI), standard deviation scores (SDS) of height, and BMI were calculated. The physical examination findings (heart rate, systolic and diastolic blood pressure, presence of goiter, ophthalmopathy, tremor, and pubertal status (pre-pubertal and pubertal) at the time of admission were recorded. Systolic and diastolic blood pressures were assessed according to reference values determined by age and gender. Hypertension was defined as blood pressure above 95th per centile of normal for age and gender. Pulse pressure was defined as the difference between systolic and diastolic blood pressure, and >40 mmHg was accepted as an increased pulse pressure.[4]

The study was approved by the Necmettin Erbakan University Non-pharmaceutical and Non-medical Device Research Ethics Committee (date: 15.01.2018; number: 1164).

Clinical, Laboratory, and Radiological Evaluations

Exophthalmos on physical examination, retraction of the upper eyelid, and presence of at least one of the lid lag findings were accepted as ophthalmopathy.[5] Ophthalmopathy was assessed according to the evaluation of a pediatric endocrinologist who subjectively examined the patient. Pubertal status was assessed according to Tanner staging.[6,7]

The free triiodothyronin (fT3), free thyroxine (fT4), and TSH levels of the patients at diagnosis were recorded. The reference values were; fT3: 2.5-5.2 pg/mL, fT4: 0.97-1.67 ng/dL, TSH: 0.27-4.2 µIU/mL.[3] TSHRAb, anti-thyroid peroxidase antibody (antiTPO), and antitiroglobulin antibody (antiTG) levels were recorded as thyroid autoantibodies. Thyroid ultrasonography (thyroid gland size, parenchymal echogenicity, presence of nodule) and thyroid scintigraphy results were recorded. Thyroid volume for each lobe was calculated according to measurements on ultrasonography using the formula: height width depth 0.529. The arithmetic sum of the volume of both lobes was used to determine the total volume of the gland. The volume of the thyroid gland was assessed by comparison with the reference values of World Health Organization according to age and gender.[8]

Definitions

Hyperthyroidism was defined as an increase in fT3 and/or fT4 levels and suppression of TSH levels with clinical findings. Euthyroidism was defined as serum TSH, fT4, and/or fT3 levels within the normal reference range.[3] The diagnosis of Graves' disease was established by the presence of clinical and laboratory findings of hyperthyroidism, positive TSH receptor antibodies, and/or ophthalmopathy. The diagnosis of Hashimoto thyroiditis was established by clinical findings of hyperthyroidism and the absence of TSH receptor antibodies, increased thyroid autoantibody levels, and/or the presence of goiter and the presence of increased thyroid echogenicity on ultrasonography.[1] Clinical and biochemical euthyroid status at least 1 year after the discontinuation of antithyroid drug therapy or clinical and biochemical hypothyroidism without antithyroid drug therapy was defined as remission. Relapse was defined as the reappearance of signs and symptoms of hyperthyroidism after at least 18 months of antithyroid drug therapy.[1]

Statistical Analysis

Statistical analyses were performed using SPSS software version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, version 19.0. Armonk, NY: IBM Corp.) Categorical data were presented with n and %, and numerical data with mean ± standard deviation if normally distributed, and median (IQR) if non-normally distributed.

Results

Thirty-one (79.5%) patients were female. The median age at admission was 14.4 (4.3-17.5) years. The demographic and clinical data of the patients are summarized in **Table 1**. Thirty-one (79.5%) patients were in the pubertal period. In 9 (23.1%) patients, there was a consanguineous marriage between parents. Thirteen (33.3%) patients had a family history of autoimmune thyroid disease. Down syndrome in 1 patient, asthma in 1 patient, and type 1 diabetes mellitus in 1 patient were accompanying diseases.

Thirty-three (84.6%) patients with hyperthyroidism had Graves' disease, and 6 (16.7%) had Hashimoto

thyroiditis. The most frequent complaints of the patients were nervousness (n=24, 61.5%), palpitation (n=22, 56.9%), sweating (n=21, 53.8%), weight loss (n=20, 51.2%), and fatigue (n=19, 48.7%). Other symptoms included heat intolerance, swelling in the neck, tremor, increased appetite, exophthalmos, attention deficit, hyperactivity, and sleep disturbance.

The most frequent physical examination findings in patients with hyperthyroidism was goiter in 31 (79.5%) patients, tachycardia in 27 (69.2%) patients, increased pulse pressure in 23 (59%) patients, and exophthalmos in 15 (38.5%) patients.

Median heart rate was 110 beats/min, mean systolic blood pressure was 107.5±15.2 mmHg and mean diastolic blood pressure was 67.5±14.0 mmHg. In 3 (8.3%) patients, systolic blood pressure was above 95th percentile. The median BMI SDS of patients with hyperthyroidism was 0.02 (-2.13; 1.50) and the median height SDS was 0.15 (-2.38; 2.60).

The median fT3 level of the patients was 9.76 (4.92-27.67) pg/mL, median fT4 level was 4.55 (1.43-9.02) ng/dL, and median TSH level was 0.035 µIU/mL (0.0006-0.85). TSH was suppressed in all patients, fT3 level was increased in 94.4%, and fT4 level was increased in 80.5% of them. In patients with Graves' diseases, TSHRAb levels were found to be positive in 31 (93.9%) patients. Thyroid microsomal antibody level was positive in 20 (60.6%) patients and antithyroglobulin antibody were positive in 23 (69.7%) patients. In 33 patients with Graves' diseases, at least one of the thyroid autoantibodies was positive.

The thyroid ultrasonography was normal in 7 (19.4%) patients, the parenchyma was heterogeneous and the gland was enlarged in 29 (74.4%) patients, and parenchymal fibrosis was present in 3 (7.7%) patients. Hyperactive diffuse involvement was detected in 13 (81.2%) of the 16 patients who underwent thyroid scintigraphy, and mild involvement was detected in 3 (18.8%) patients.

All patients were initially treated with antithyroid drug therapy, and in 21 (53.8%) patients, a tachycardia beta-blocker was also administered. At the time of first diagnosis, 35 patients were administered methimazole (MTZ) and 4 patients were administered propylthiouracil (PTU) therapy (**Table 2**). The median MTZ dose was 20 mcg (15-30 mcg) at baseline and follow-up. Antithyroid drug therapy was discontinued at the median 9th month (2-33 months). Six of the patients who were taking MTZ therapy were transferred to the adult endocrine unit at the age of 18. In 9 patients, antithyroid therapy was ongoing, and the median follow-up duration was 13 months (3-26 months). Total thyroidectomy was performed in two patients who were unresponsive to antithyroid drug treatment and had advanced goiter at the 18th and 30th months of treatment. No significant relationship was found between antithyroid drug doses and thyroid hormone levels, and remission and remission periods. RAI treatment was administered to three patients. A total of 9 patients were started on thyroid hormone replacement. This included 4 patients with Hashimoto's thyroiditis, 3 patients after RAI treatment, and 2 patients after total thyroidectomy. In one of them, the reason was neutropenia due to PTU and unresponsiveness to drug treatment. In one patient, MTZ treatment was switched to PTU due to drug rash. The most recent status of seven patients who did not continue follow-up could not be determined.

In our study, adverse effects of antithyroid drugs were detected in 7 patients (21.2%), including MTZ-induced agranulocytosis and widespread rash, 2 cases of rash, 2 cases of mild transaminase elevation, and 1 case of mild thrombocytopenia. The remaining 5 cases were mild and did not require drug discontinuation.

Highlights

- Hyperthyroidism is a rare thyroid gland disease caused by increased levels of thyroid hormones in childhood.
- Graves' disease is by far the most common cause of hyperthyroidism in children and adolescents, is more common in females, and usually presents during adolescence.
- Clinical manifestations of hyperthyroidism include modest acceleration of linear growth and epiphyseal maturation, weight loss or failure to gain weight, excessive retraction of the eyelids causing lid lag and stare, tachycardia and increased cardiac output, increased gastrointestinal motility, proximal muscle weakness, tremor, hyperreflexia, sleep disturbance, distractibility with unexplained poor school performance, and emotional lability.

Discussion

Hyperthyroidism is a rare condition in children, and the most common cause is Graves' disease. It especially peaks during adolescence. The gender distribution of Graves' disease is 5/1, in favor of females.[1] The most common cause of hyperthyroidism in our study was Graves' diseases while Hashimoto thyroiditis was the second. The median age of the patients was 15.7 years, and 80.5% of them were female. Four-fifths of the cases were diagnosed in the pubertal period. The age and gender distribution of the patients was found to be consistent with the literature.

Symptoms and signs may be minimal in the early stages of the disease because the establishment of the disease could take months. Usually, the first signs are changes in behaviors and failure in school. Insomnia, restless sleep, and nocturia are frequently observed and are usually associated with fatigue and lethargy during the daytime. In addition, palpitations, frequent defecation, and increased sweating are common symptoms.[1,9] In our patients, it was thought that the first complaints were ignored and they were usually admitted when more disturbing findings emerged, such as nervousness and palpitations. When we evaluated retrospectively, we found that behavioral changes and failure in school were frequent.

Graves' diseases is an immunogenetic disease, and 60% of patients have a family history of autoimmune thyroid disease. It has been shown that there is a relationship between Graves' disease and a single nucleotide polymorphism in the *PTPN22* gene on

chromosome 1p13. The concordance rate between monozygotic twins is 20-60%, which indicates the role of environmental factors in the development of disease.[10-12] In our study, family history of autoimmune thyroid disease was 33%, which is less than that reported in the literature. Graves' disease may be accompanied by autoimmune diseases such as Hashimoto thyroiditis, vitiligo, systemic lupus erythematosus, rheumatoid arthritis, Addison's disease, myasthenia gravis, type 1 diabetes mellitus, and pernicious anemia.[13] One of our patients was diagnosed with type 1 diabetes mellitus in addition to Graves' diseases.

Thyromegaly (goiter) is present in many patients.[14] The thyroid gland usually grows symmetrically and is smooth, soft, and painless. A palpable thrill or audible murmur may be present, indicating increased blood flow in the gland. In our study, the most common finding was goiter.

Table 1.
Demographic data and clinical findings of the patients with hyperthyroidism

Age, month (median, range)	4.4 (4.3-17.5)
Gender, female, n (%)	31 (79.5)
BMI, SDS (median, range)	0.02 (-2.13;1.50)
Height, SDS (median, range)	0.15 (-2.38;2.60)
Heart rate, min (median, range)	110 (82-148)
Systolic blood pressure, mmHg (mean ± SD)	107.5±15.2
Diastolic blood pressure, mmHg (mean ± SD)	67.5±14.0
Complaints, n (%)	
Nervousness	24 (61.5)
Palpitation	22 (56.9)
Sweating	21 (53.8)
Weight loss	20 (51.2)
Fatigue	19 (48.7)
Heat intolerance	13 (33.4)
Neck swelling	11 (28.2)
Tremor	9 (23.1)
Eye edema	9 (23.1)
Others	7 (17.9)
Physical examination findings, n (%)	
Goitre	31 (79.5)
Tachycardia	27 (69.2)
Increased pulse pressure	23 (59)
Exophthalmos	15 (38.5)
Laboratory	
Free T3 pg/mL	9.76 (4.92-27.67)
Free T4 ng/dL	4.55 (1.43-9.02)
TSH µIU/mL	0.035 (0.0006-0.85)
TSHRAb positivity n (%)	32 /33 (97)
Anti-thyroid peroxidase antibody positivity, n (%)	20/33 (60.6)
Antitiroglobulin antibody positivity, n (%)	23/33 (69.7)

BMI; Body mass index, SDS; Standard deviation scores, SD; Standard deviation, T3; Triiodothyronin, T4; Thyroxine, TSH; Thyrotropin, TSHRAb; TSH receptor antagonist

Table 2.
Treatment modalities and recent status of patients

Treatment/recent status	n (%)
Antithyroid drug (initial); Methimazole Propytiouracil	 35 (89.7) 4 (11.3)
β-blocker	21 (53.8)
Radioactive iodine	3 (7.7)
Surgery	2 (5.1)
Antithyroid drug users who are in remission	10 (25.6)
Follow-up without treatment	6 (15.4)
Patients who developed hypothyroidism and are receiving L-thyroxine treatment	9 (23.1)
Transferred to adult endocrine unit	7 (17.9)
Not continuing follow-up	7 (17.9)

More than half of children and adolescents with Graves' disease may have ophthalmic abnormalities. In most patients, signs and symptoms are relatively mild. These include; lid lag, retraction in the lid, proptosis, conjunctival injection, chemosis, periorbital edema, and less frequent pain in the eye, restlessness, and diplopia.[15,16] Exophthalmos was present in 36.1% of our patients. Because ophthalmopathy is mild in childhood, it is usually self-limiting and does not require treatment. Eye symptoms usually regress after controlling hyperthyroidism. Rarely, symptomatic treatment is needed, such as oral corticosteroids, orbital radiation, and surgical decompression. In our study, symptomatic treatment was not required for patients with eye findings.

In almost all hyperthyroid patients, serum TSH levels are either too low or unmeasurable.[1,17] In our study, TSH was suppressed in all patients, consistent with the literature, and the median level was 0.035 μIU/mL (0.0006-0.85). The number of patients with increased fT3 levels was greater than the number of patients with increased fT4 levels, similar to the literature. TSHRAb positivity was detected in 93.8% of patients with Graves' diseases. In Graves' diseases, thionamide treatment reduces TSHRAb levels via an immunomodulatory effect. Two patients with negative TSH receptor antibody had been given antithyroid treatment, which may be the reason for this negativity. In addition, Graves' disease with negative TSHRAb levels has also been reported.[18,19]

Hyperthyroidism is resistant and progressive in untreated Graves' disease patients. Spontaneous remission in children with Graves' disease is very rare, approximately 30%. Low levels of TSHRAb and low thyroid gland volume may indicate remission with medical treatment. If the TSHRAb level is high and the thyroid gland is large, the spontaneous remission rate is low. There are three treatment options for children and adolescents with hyperthyroidism; medical treatment, surgical treatment, and RAI.[20] Antithyroid drug therapy is used as the first option in childhood, but its long-term use is not recommended because of the low remission rate and serious adverse effects. The drugs used for antithyroid treatment are PTU and MTZ. In the initial treatment, MTZ was administered to 35 patients and PTU was administered to 4 patients. These drugs are iodinated and degraded in the thyroid gland, thus preventing the formation of T4 and T3. These drugs may have serious adverse effects such as agranulocytosis, hepatotoxicity, and systemic vasculitis, and if these adverse effects develop, they should be discontinued immediately. In addition, urticaria, arthritis, nasal discharge, abnormal taste sensation, and pruritus are other moderate side effects. In the literature, the frequency of adverse effects is reported to be approximately 13%.[20,21] In our study, adverse effects were detected in 21.2% of patients. It was higher than that reported in the literature, and we considered that this situation could have resulted from the admission of more complicated cases to our clinic because our clinic is a reference hospital.

While RAI therapy has been used for many years in adults as a first-line treatment for hyperthyroidism, its use in children and adolescents is limited, and it is preferred as a second option in the treatment. In children and adolescents, there is a concern that free RAI administration may increase the frequency of thyroid cancer and leukemia over a long follow-up period. It has been reported that iodine doses administered for treating hyperthyroidism do not induce mutagenesis. Improvement is usually achieved within 3 to 6 months with RAI treatment, and second or third doses are rarely needed.[22,23] In our study, single-dose RAI treatment was administered to 3 patients because of adverse effects and unresponsiveness to treatment, and permanent hypothyroidism developed during follow-up.

Surgical treatment is the fastest-acting option of the treatment. Before surgery, iodine preparations are recommended for at least 10-14 days and then subtotal or total thyroidectomy is performed. Surgery is rarely recommended because of the increased use of RAI therapy in children. Nevertheless, numerous goiter, medical treatment failure, cases not accepting RAI treatment, patients under the age of 5 years and solid "cold" nodules are indications for surgical treatment.[2,17,24] In our study, total thyroidectomy was performed in two patients due to a large goiter.

Conclusion

In conclusion, although hyperthyroidism is rare in childhood, its treatment is difficult and requires close follow-up. Treatment options differ from those of adult patients, and there is a need for multicenter studies evaluating treatment efficacy and long-term outcomes.

Ethical Approval: The study was approved by the Necmettin Erbakan University Non-pharmaceutical and Non-medical Device Research Ethics Committee (date: 15.01.2018; number: 1164).

Informed Consent: Retrospective study.

Author Contributions: Kocabey Sütçü Z: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Eklioğlu BS: Surgical and Medical Practices, Design.; Atabek ME: Surgical and Medical Practices, Design, Analysis or Interpretation.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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Journal of Pediatric Academy

Original Article

Year: 2024 Volume: 5 Issue: 2
Doi: 10.4274/jpea.2024.307
J Pediatr Acad 2024; 5: 56-62

The Effectiveness of Parenting Program Based on Video Interactive Guidance

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Article Information

Article Type: Original Articles
Article Group: Pediatric Psychiatry Group Study

Received: 23.04.2024
Accepted: 01.06.2024
Epub: 07.06.2024
Available Online: 01.07.2024

Cite this article as: *Menteşe Babayiğit T, Çıkılı Uytun M, Temeltürk RD, Efendi GY, Öztop DB, Yürümez E, Üstün Güllü B, Pekacar Uyaroğlu S. The Effectiveness of Parenting Program Based on Video Interactive Guidance. J Pediatr Acad. 2024; 5: 56-62*

Abstract

This study aimed to assess the impact of a video-based interactive guidance (VIG) training program on parents' anxiety, depression levels, coping styles, and interactions with their infants. The sample comprised eight children aged 24-40 months years diagnosed with autism spectrum disorder and/or developmental delay. After the diagnostic process, the parents participated in a 4-session VIG parenting program. Pre- and post-implementation comparisons were made on various variables. Data were collected from mothers using sociodemographic forms, Beck Depression Inventory, State Trait Anxiety Inventory, The Ways of Coping Inventory, parenting attitudes styles, and Crowell procedure (PIR-GAS) scores. Our findings revealed that following VIG, the quality of parent-child relationships improved significantly compared with earlier assessments, as observed through PIR-GAS evaluations. Moreover, there was a notable decrease in ineffective coping styles among parents. The VIG outlined in this study proved to be a highly successful psychological therapy method for children and preschoolers. However, while these results are significant, evidence supporting this program's effectiveness for mothers and children in early childhood is limited, emphasizing the need for further research.

Keywords: Video-based interactive guidance, parental training, infant, relationship

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Introduction

Parents play a fundamental role in the healthy development of their infants through their abilities to perceive, understand, and manage their own and their infants' emotions.[1] Many scientific studies have illustrated how the parent-child relationship significantly influences infant perceptions and developmental processes during infancy and early childhood.[2,3] The alignment of emotional shifts within the parent-child bond lays the groundwork for the infant's future adaptive skills. Neglecting to adequately address the baby's needs during this period can result in enduring challenges that prove hard to overcome in later life.[4] In addition, the infant-parent relationship can play a protective role by reducing the negative effects of environmental risk factors that may be seen in the infant's developmental process.[5] This relational bond helps children to better regulate their negative emotions in times of stress, develop better social skills, become more confident in exploring their environment, and build the foundation for other relationships.[6] For all these reasons, the focus of infant mental health is on relationships rather than psychopathologies.[7]

In this context, it is important to identify the early antecedents and risk factors of developmental deviations based on relationship problems.[6] The parent-child relationship is acknowledged as a significant risk factor for the onset of early psychopathology.[8] However, what is even more significant is that parenting can be modified and molded. Therefore, parent training programs to improve parenting early on, when all the child's biological systems are rapidly forming, are likely to be effective for both aspects of the relationship.[9] Parenting programs stand as the primary early intervention strategy for addressing child mental health and behavioral issues. These parent training programs mainly improve parents' ability to recognize, interpret, and respond appropriately to their children's signals.[10]

Interventions employing video feedback techniques enhance children's behavior by fostering heightened parental sensitivity. These interventions typically involve observing parents and infants engaging in play together, with subsequent review sessions conducted with a therapist to emphasize positive interaction moments.[11] In our infant mental health outpatient clinics, the video interaction guidance (VIG) program is used most often. Despite being a commonly used intervention program, there are few pilot studies and limited data regarding its effectiveness. The aim of this study was to evaluate the effectiveness of this method on the mother's mental state, coping styles, and parenting attitudes.

Material and Method

Procedure

In this study, eight children aged 24-40 months who were admitted to the Ankara University Infant Mental Health Unit and diagnosed with autism spectrum disorder and/or developmental delay were included.

Approval was obtained from the Human Research Ethics Committee of Ankara University (date: 25.04.2024 and decision number: İ03-283-24) to examine and analyze the psychiatric and psychometric evaluation results of the included infants and mothers. Informed consent was not required for our study because the available data for these evaluations, which we routinely perform in Ankara University Infant Mental Health Unit, were retrospectively analyzed. After obtaining detailed medical histories from the parents of infants who presented to our clinic and completing a sociodemographic data form, the Crowell procedure was administered. Infants were diagnosed using the DC 0-3 diagnostic system during Crowell assessment. The evaluation team assessed the infant-parent relationship for the necessity of intervention. After the diagnostic procedure, the parents of the participants engaged in a four-session parenting program based on interactive guidance. The groups were assessed before and after program implementation to compare variable rates. As part of the research study, comprehensive data on mothers' mental states, coping methods, and attitudes toward their children were gathered using various instruments. These tools included the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI), the Ways of Coping Inventory (WOC), and the Parental Attitude Research Instrument (PARI).

Measures

Sociodemographic Data Form

This structured questionnaire was designed by the researchers to collect information about the social and demographic characteristics of the participants. The researcher filled out this form with the information received from the parents.

Beck Depression Inventory

The BDI is a widely recognized self-report questionnaire that consists of 21 questions with scores ranging from 0 to 63 points and is used to measure the severity of depression.[12] Over the years, the psychometric properties of the BDI have been extensively evaluated, demonstrating its reliability and validity in assessing depressive symptoms.[13,14] The BDI has been widely used in various settings, including medical patients,[15] psychiatric outpatients,[16] and caregivers of individuals with specific health conditions.[17] Higher BDI scores indicate more severe depressive symptoms.[18] The psychometric properties of the Turkish version of the BDI have been evaluated with respect to other scales, demonstrating good convergent and discriminant validity.[19] A Turkish validation and reliability study of the BDI was conducted by Hisli, further solidifying its usefulness in evaluating depression levels in the Turkish population.[20] This assessment scale was used to evaluate the depression symptoms of the mothers included in our study.

The State-Trait Anxiety Inventory

The STAI is a widely used tool for assessing anxiety in various populations. It consists of two subscales: The State Anxiety Inventory and the Trait Anxiety Inventory, each containing 20 items. The scores on the STAI range from 20 to 80, with higher scores indicating higher levels of anxiety.[21] STAI differentiates between temporary state

anxiety and stable trait anxiety.[22] It has been validated and shown to have good psychometric properties, including internal consistency and reliability.[23] The STAI has been adapted into Turkish, showing good reliability with Cronbach's alpha coefficients ranging from 83 to 96.[24] This assessment scale was used to evaluate the anxiety symptoms of the mothers included in our study.

The Ways of Coping Inventory

The WOC is a well-established psychological tool used to evaluate coping strategies in various populations facing different stressors. Initially developed by Lazarus and Folkman in 1984, the inventory has been tailored for specific contexts such as cancer patients.[25] It comprises 30 items and encompasses subscales like self-confidence, optimism, submissiveness, helplessness, and seeking social support.[26] The WOC has been applied in research focusing on coping with diverse challenges, and the Turkish version of the WOC has been utilized in research comparing stress responses between migraineur and non-migraineur women, showing its applicability in studying stress-related phenomena.[27] This assessment scale was used to determine the methods of coping with stress factors of the mothers included in our study.

Parental Attitude Research Instrument

The PARI is a Likert-type attitude scale developed by Schaefer and Bell in 1958.[28] This instrument consists of 115 items and has been widely used to assess parental attitudes toward various aspects of child rearing and family life. The PARI has been utilized in diverse studies to evaluate parental attitudes on topics such as child care, parenting skills, resilience, dental fear, and attitudes toward specific disorders like Internet gaming disorder and asthma medication adherence.[29] This assessment scale was used to evaluate the attitudes and behaviors of the mothers included in our study toward their children.

Crowell Procedure

The Crowell procedure is a method designed to assess the interaction between caregivers and children in a clinical setting, specifically targeting children aged approximately 12-60 months.[30] This procedure involves observing and evaluating the problem-solving behavior of both the caregiver and the child during a semi-structured interaction.[31] This study aims to provide insights into the dynamics of the caregiver-child relationship and can be used to predict subsequent interactions between the mother and child, as well as internalize symptomatology in children.[32] The Crowell procedure is considered a formal assessment tool for parent-child interactions, offering a structured approach to evaluating the quality of these interactions.[33]

Highlights

- It is important to evaluate the parent-infant relationship during intervention for mental health problems in infancy.
- The video-based interactive guidance (VIG) program is one of the most important parenting programs implemented in clinical practice and has been demonstrated to be effective.
- The VIG program enhances parents' ability to understand and respond appropriately to signals from their infants.

Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood (DC:0-3)

This classification is a multiaxial diagnostic system used for psychiatric evaluations of children under the age of 3. It comprises the clinical disorder of the infant (Axis I), relationship classification (Axis II), which underscores the pivotal role of the parent-infant relationship, medical and developmental disorders and conditions (Axis III), psychosocial stressors (Axis IV), and emotional and social functioning of the infant (Axis V). In the DC: 0-3 classification system, the parent-infant relationship global assessment scale (PIR-GAS) assesses the quality of the parent-child relationship, considering the frequency, intensity, and duration of maladaptive interactions. Scores range from 10, indicating gross impairment, to 90, representing highly functional relationships. Scores below 40 signify a disordered relationship.[34]

Interactive Guidance-Based Parenting Program

VIG is a method that offers guidance and support to parents in establishing positive contact and attunement with their infants. Its effectiveness has been proven to promote secure attachment between parents and children, reduce parental stress, and improve child development outcomes. VIG is a flexible intervention that can be adapted to various settings and cultural contexts, making it a valuable tool for promoting positive parent-child relationship worldwide.[35] The VIG method uses edited video feedback to help parents recognize their strengths and reaching their desired objectives. VIG interventions typically consist of 3-5 sessions and involve adopting a collaborative and empowering approach toward the parents and providing a framework of theoretically derived communication/contact principles to analyze interactions. The edited film elements provide feedback on "positive exceptions", facilitating reflection and developing parental self-efficacy by discussing these self-modeling examples.

Statistical Analysis

The data analyses were conducted using Statistical Package for Social Sciences version 23.0, with p-values <0.05 considered statistically significant. The study data were evaluated using the Wilcoxon signed rank test.

Results

Sociodemographic Characteristics of the Children

The study sample comprised eight children, consisting of two females and six males, with ages ranging from 24 to 40 months. The sociodemographic characteristics of the cohort encompassing parental features, family type, and clinical diagnoses of children are presented in **Table 1**.

Comparisons of psychiatric assessment tools between pre- and post- parental intervention are summarized

in **Table 2** (Wilcoxon signed ranked test). In the observational assessment of caregiver-child interaction using PIR-GAS before and after video interactive guidance, it was found that following this parenting program, the quality of parent-child relationship was higher than that before assessments. Additionally, psychiatric assessment scale scores revealed a decrease in parental depression and anxiety levels after the intervention; however, there was no statistically significant difference. Similarly, although a slight decrease was observed in the subscales of parental attitude styles, these changes were not statistically significant. Nevertheless, when comparing the coping strategies of parents, significant improvements were detected, particularly in ineffective style scores.

Discussion

The aim of this study was to evaluate the levels of depression, anxiety, perceptions and attitudes toward their infants, and coping styles of mothers with infants having different psychopathologies before and after a parenting program based on interactive video guidance. Our study findings suggest that the video-based interactive guidance program may have a positive impact on parents' coping skills and interactions with their infants.

The evidence supporting the effectiveness of VIG in enhancing interaction between parents and their children is increasingly growing.[36,37] A meta-analysis of 20 studies (involving 1757 parent-child pairs) on the effectiveness of this parent education and intervention program reported results indicating an increase in

Table 1.
Sociodemographic and clinical characteristics of children

Variables	Children (n=8) mean ± SD (min-max)/n (%)
Gender, n (%)	
Female	2 (25)
Male	6 (75)
Child age (months)	32.25±5.47 (24-40)
Mothers' age (years)	35.24±4.99 (24-44)
Fathers' age (years)	41.50±3.77 (35-47)
Mothers' education level (years)	13.50±1.77 (12-16)
Fathers' education level (years)	14.50±2.77 (8-16)
Number of siblings	0.75±0.70 (0-2)
Family type, n (%)	
Intact family	8 (100)
Psychiatric diagnosis, n (%)	
Intellectual disability	3 (37.5)
Autism spectrum disorder	2 (25)
Intellectual disability + autism spectrum disorder	3 (37.5)

SD; Standard deviation, Min; Minimum, Max; Maximum

Table 2.
Comparison between the pre- and post-treatment scores of psychiatric assessment tools

Assessment tools	Pre-treatment median (IQR)	Post-treatment median (IQR)	P value*
Observational scores			
PIR-GAS	40 (30-50)	60 (57.5-72.5)	**0.038**
Scales scores			
BDI	15 (7.5-18.75)	7.5 (3.25-16.75)	0.293
STAI-state	41 (29.5-59.5)	36.5 (25.5-51.5)	0.292
STAI-trait	43.5 (37-58.75)	42.5 (31-54.25)	0.292
STAI-total	84.5 (68.75-113.25)	77 (58.5-105.75)	0.237
The Ways of Coping Inventory			
Effective coping styles	33 (30-42)	32.5 (30.5-36.75)	0.248
Ineffective coping styles	15.5 (11.75-26.75)	9 (4.25-14.5)	**0.027**
Parental attitude research instrument			
Democratic	69 (36.5-78)	68.5 (29.5-74.75)	0.674
Authoritative	22.5 (18-40.25)	17 (15.25-41.25)	0.623
Permissive	27.5 (22.5-33)	27.5 (22.5-33)	1
Protective	33.5 (20-38.5)	31.5 (21.75-34.5)	0.606

IQR; Interquartile range, PIR-GAS; Parent infant relationship- global assessment scale, BDI; Beck Depression Inventory; STAI; State-Trait Anxiety Inventory
The characteristics of non-normally distributed variables, median (IQR), serve as representative measures.
Bold values indicate statistical significance.
* Wilcoxon signed rank test

parental sensitivity up to 6 months post-intervention. The meta-analysis of two studies (involving 166 parent-child pairs) reported results indicating an increase in the likelihood of secure attachment after intervention. The meta-analysis of two studies (involving 119 parent-child pairs) with long-term follow-up periods found no evidence of effectiveness on children's behavior. In addition, there is insufficient evidence to suggest a significant effect of interactive guidance programs based on video feedback on parental stress or anxiety.[36,38,39] When interpreted in the context of sample sizes, diversity of measurement tools, and differences in follow-up periods, these findings suggest a need for further evidence regarding the impact of interactive guidance programs based on video feedback on longer-term outcomes such as attachment and children's behavioral outcomes. However, research consistently indicates that early and targeted intervention programs can be effective tools for increasing parental sensitivity and improving parenting behaviors and attitudes.[36,39] The result presented in the meta-analysis, indicating a reverse relationship between the duration of the program and its effectiveness on parenting behavior, is quite intriguing and deserves further investigation through long-term follow-up studies.[36]

In our study, a positive improvement was observed in the PIR-GAS scores measuring parent-infant interaction following VIG. However, no significant change was observed in parents' attitudes toward their infants. Barlow and McMillan,[40] in their study evaluating parental attitudes, demonstrated that VIG is particularly beneficial in preventing the emergence and recurrence of emotional maltreatment in parents. The process leading to this effect is primarily described as interpersonal. In interactive guidance programs based on video feedback, the focus is not solely on the experience of the child or the parent, but rather on what is happening between these individuals. By promoting a dialogical structure that encourages mentalization, parents can mutually experience creating space in their minds for their baby and understanding how this affects their baby's mind.[41] Throughout this process, it is assumed that a series of metacognitive changes may be observed stemming from the inconsistency between parents' beliefs about parenting skills and what they can see in the video. Additionally, an increase in self-efficacy and reflective skills is expected.[38]

According to our study findings, no significant change was observed in the levels of depression and anxiety among parents before and after VIG. It is highly likely that all the infants we evaluated have a potentially persistent psychopathology, and there is a possibility that their parents may have developed depression or anxiety disorders as a result. This could reduce the effectiveness of the implemented program and could be a factor influencing our findings. Depression can limit a parent's emotional availability and therefore have both short-term and long-term negative effects on the child's emotional, social, cognitive, and physical development.[42] Additionally, mothers with depression are more likely to report parenting stress and have more intense negative perceptions of their infants' behaviors.[43] Interventions aimed at reducing maternal depression levels do not always have a direct effect on the interaction between the mother and child. Feedback received following a group intervention using VIG to reduce postpartum depression in mothers has shown an increase in mothers' awareness and enjoyment in their relationships with their babies, as well as a decrease in their depression while becoming more attuned to their child.[44] Several studies evaluating the use of VIG in preterm infants have shown improvement in parents' sensitive behaviors and a decrease in withdrawn behaviors, but no change in intrusive attitudes.[11,45]

Another important point emphasized in studies evaluating the effectiveness of VIG and similar intervention programs is the presence of accompanying risk factors in the family system. VIG programs focusing on parent-child interaction are particularly successful in alleviating parental stress in the context of interaction difficulties (i.e., at the parent-child level). However, their impact may be lower in addressing other significant issues at the parent level (such as maternal depression) or at the family level (such as poverty, isolation).[36] Conversely, certain studies indicate that this method is notably effective in families facing significant challenges, such as those affected by domestic violence, adult mental health issues, and parental substance abuse.[46] Consequently, parent intervention programs targeting families with significant accompanying risk factors should be an integral part of a comprehensive treatment process.

VIG is recognized today as an evidence-based intervention program. It has been recommended as an effective method in the National Institute for Health and Care Excellence guidelines and the Wave Trust's overview of effective interventions from pregnancy to age 2.[47,48] It is currently widely implemented in different countries around the world.[49] This intervention program appears to be a promising method not only for parents but also for educators working with infants and young children in enhancing their social and emotional support for children.[50] Comprehensive follow-up studies on this topic will enhance our current knowledge.

Study Limitations

This study has several limitations. First, our sample size was insufficient to generalize the findings. The results need to be confirmed in larger samples. Furthermore, in our study, the effectiveness of the video-based interactive guidance program was evaluated in infant-mother dyads with different psychopathologies. To eliminate the effect of possible confounding factors related to psychopathology, evaluation in a more homogeneous group may provide important results.

Conclusion

Our research reveals evidence of favorable alterations in parent-infant interaction and a reduction in parents' ineffective coping strategies following participation in the video-based interactive guidance program. Reflecting on advancements thus far, addressing infant mental health within the framework of their primary relationships, with a focus on relationships, holds

significant importance in comprehending the onset of psychopathology. Consequently, parenting education programs implemented in clinical settings are poised to serve as effective interventions within broader systems that encompass both infants and their parents.

Ethical Approval: The study was approved by the Ankara University Human Research Ethics Committee (date: 25.04.2024 and decision number: İ03-283-24).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Author Contributions: Menteşe Babayiğit T: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Çıkılı Uytun M: Concept, Design, Data Collection or Processing, Literature Search.; Temeltürk RD: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Writing.; Efendi GY: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Writing.; Öztop DB: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search.; Yürümez E: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search.; Üstün Güllü B: Concept, Design, Data Collection or Processing, Analysis or Interpretation.; Pekacar Uyaroğlu S: Concept, Design, Data Collection or Processing, Analysis or Interpretation.

Conflict of Interest: The authors declare no conflicts of interest. The authors are responsible for the content and writing of this article.

Financial Disclosure: The authors declared that this study received no financial support

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Journal of Pediatric Academy

Original Article

Year: 2024 Volume: 5 Issue: 2
Doi: 10.4274/jpea.2024.265
J Pediatr Acad 2024; 5: 63-69

Clinical Profile, Laboratory Characteristics and Treatment of Wilson's Disease in Children from Western India

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Article Information

Article Type: Original Articles
Article Group: Pediatric Gastroenterology

Received: 24.10.2023
Accepted: 07.06.2024
Epub:
Available Online: 01.07.2024

Cite this article as: *Vajpayee S, Goyal AK, Yadav Y, Agarwal R. Clinical Profile, Laboratory Characteristics and Treatment of Wilson's Disease in Children from Western India. J Pediatr Acad. 2024; 5: 63-69*

Abstract

To study the clinical profile and laboratory characteristics and treatment of children with Wilson's disease (WD). The current study was done at Department of pediatrics, Sir Padampat Institute of Neonatology and Pediatric Health, Sawai Man Singh Medical College, Jaipur. It was an observational study and institution ethics committee approved the study. Patients visiting the outpatient department or admitting in wards with clinical presentation suggestive of WD were enrolled in the study after obtaining a valid informed written consent. Patients subjected to detailed clinical history and physical examination. All patients subjected to routine blood count, biochemistry including liver function tests and specific laboratory investigations. They underwent ophthalmological examination. Ultrasonography abdomen and liver biopsy performed in enrolled patients. Magnetic resonance imaging brain carried out in patients with neurological WD. Ferenci score was calculated for each of the patients. Total 50 patients were included in the study. Mean age at the time of diagnosis was 9.4 years with delay of 11 months after onset of symptoms. Male is to female ratio was 2/1. Hepatic manifestation were seen in 76% patients and 24% patients presented with neurological disease. Kayser-Fleischer ring was seen in 44% patients with hepatic disease and 83% patients with neurological disease. Twenty-four hour urinary copper was more than 2 time of upper limit of normal in all patients. Fifty-four percent patients showed improvement with chelation therapy and 9 patients died during the study period. WD in children has varied clinical manifestation and early diagnosis is necessary for good prognosis. It requires wide range of tests as genetic testing is not easily available. Acute liver failure has high mortality. Early chelation therapy reverses the clinical and biochemical abnormalities.

Keywords: Wilson's disease, KF ring, liver failure, ceruloplasmin, penicillamine

Introduction

Wilson's disease (WD) is a genetic disorder with autosomal recessive inheritance. Kinnier Wilson first described the disease as "progressive lenticular degeneration" in 1912.[1] The term "hepatolenticular degeneration" was first used by Hall in 1921. The *ATP7B* gene responsible for WD identified in 1993.[2] Loss of *ATP7B* gene function is responsible for various manifestation of WD. There is decrease biliary excretion of copper due to failure of incorporation of copper into ceruloplasmin. Copper get accumulated in the liver,

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brain and other tissues that results in liver toxicity and other clinical presentation of the disease.[3,4]

The global prevalence of WD varies from 1/30,000 to 1/50,000. Some studies have suggested prevalence of 1 in 7,000.[5,6] Studies had reported genetic prevalence of heterozygous carrier frequencies as high as 1/25 to 1/53.[7,8] Delayed diagnosis and untreated disease is responsible for high morbidity and mortality due to hepatic failure and/or severe neurological disability. Therefore, early diagnosis and proper treatment is necessary for better prognosis. Walshe proved treatment with chelators as D-penicillamine (DP) in 1956 and trientene 1969 to be successful.[9,10]

There are few studies from India on pediatric WD.[11,12] Other studies describe the neurological WD in adult population.[13-15] We carried out this study to highlight the clinical features and laboratory parameters of WD in children along with treatment of the patients.

Material and Method

The current study was done at department of pediatrics, Sir Padampat Institute of Neonatology and Pediatric Health, Sawai Man Singh Medical College, Jaipur. Office of the Ethics Committee Sawai Man Singh Medical College and Attached Hospitals, Jaipur (decision no: 814, date: 26.08.2021) approved the study. It was an observational study carried out from January 2017-December 2022.

Patient Selection

Patients visiting the outpatient department or admitting in wards with clinical presentation suggestive of WD were enrolled in the study after obtaining a valid informed written consent. All patients subjected to detailed clinical history and physical examination. All patients subjected to routine blood count, biochemistry including liver function tests and specific laboratory investigations. They underwent ophthalmological examination including slit lamp examination for evaluation for Kayser-Fleischer (KF) ring and other ophthalmological findings. Ultrasonography (USG) abdomen performed to know the liver echo texture and the type of cirrhosis. Liver biopsy performed in enrolled patients. Magnetic resonance imaging (MRI) brain carried out in patients with neurological WD. Patient meeting the diagnostic criteria were included in the study. Ferenci score was calculated for each of the patients.[16]

Diagnostic Criteria

Presence of History and clinical features suggestive of WD (hepatic or neurological) plus any two of the following with or without positive family history of WD:

1) Presence of KF ring on ophthalmological evaluation.

2) Increased baseline 24-hour urinary copper excretion more than 100 µg/day in absence of acute hepatitis

3) Increased 24-hour urinary copper excretion with penicillamine challenge (PCT) more than five times of upper limit of normal (ULN) in equivocal cases.

4) Low serum ceruloplasmin, less than 20 mg/dL.

5) MRI brain suggestive of WD.

Definitions

Hepatic Disease

Presence of hepatic dysfunction defined as, clinically, presence of stigmata of liver disease-jaundice, edema, ascites, HSM, etc., plus laboratory findings suggestive of deranged liver function tests:

1) Elevated liver aminotransferases: >2 x ULN

2) Deranged Prothrombin time international normalized ratio (INR) >1.5 not corrected with vit K

3) Hypoalbumenia: Serum albumin <3.5 g/dL

4) Hyperbilirubinemia: Serum bilirubin >1.5 mg/dL

Acute Hepatitis

Presence of liver disease (clinically or biochemically) of duration less than 3 months.

Acute Liver Failure (ALF)

Pediatric ALF defined as (a) evidence of liver dysfunction within 8 weeks of onset of symptoms, (b) uncorrectable coagulopathy with INR >1.5 in patients with hepatic encephalopathy, or INR >2.0 in patients without encephalopathy, and (c) no evidence of chronic liver disease either at presentation or in the past.[17]

Chronic Liver Disease

Presence of liver disease (clinically or biochemically) of duration more than 3 months.

Cirrhosis

Radiological (USG) findings of heterogeneous liver with coarse echo texture with nodule formation and irregular borders. Histopathologically, characterised by progressive hepatic fibrosis, distortion of hepatic architecture, and presence of regenerative nodule.

Copper Study

Serum Ceruloplasmin

Done by immunoturbidometry by COBAS automated instrument. Normal values 20-60 mg/dL.

Urinary Copper

Done by DI-Br-PAESACOMPLEXONE/SPECTRO photometry. UV-1800 SPECTROPHOTOMETER INSTRUMENT was use. Normal values 0-40 µg/day.

We do not carried out liver copper estimation and genetic testing of patients due to non-availability of these investigations at our centre.

Statistical Analysis

Statistical analysis was done using computer software (SPSS Trail Version 23 and primer). The qualitative data were expressed in proportion and percentages and the quantitative data was expressed as mean and standard deviations. The difference in proportion was analysed using the Student t-test. 5% probability level as considered as significant, i.e, p-value <0.05.

Results

Total 50 patients were included in the study. Mean age at the time of diagnosis was 9.4 years with delay of 11

months after onset of symptoms. Male is to female ratio was 2/1 with 35 boys and 15 girls. Family history for liver disease was positive in 20 percent patients and history of consanguinity in 20%. Five patients diagnosed on family screening. Youngest patient was three-year-old presented with acute hepatitis with serum ceruloplasmin level of 19 mg/dL and 24-hour urinary copper was 934. Oldest patient was of 16 years admitted with decompensated chronic hepatitis.

Mode of presentation enumerated in **Table 1**. Among patients with neurological WD, 50% were older than 10 years. Two patients with hepatic WD presented with hemolytic anemia, two with effusion of knee joint. One patient was having hydronephrosis with renal calculus. He was also having neuroregression and history of jaundice in past. KF ring was positive in this patient and with serum ceruloplasmin 16 mg/dL. Baseline 24-hour urinary copper was elevated to 332 µg/day. USG abdomen showed coarse echotexture with micronodular cirrhosis. MRI brain showed hyper-intensities in basal ganglia on T2 images.

Table 2 shows the clinical and biochemical profile of patients. Twenty-one (61.7%) patients were having aspartate aminotransferase (AST) more than two times ULN whereas alanine aminotransferase (ALT) was more than two times ULN in fourteen (41.1%) patients. AST/ALT ratio was more than two in eleven patients.

Table 3 shows diagnostic indices and follow up of patients along with comparison of hepatic and neurological WD. KF ring was positive in 54% (27) of all patients. The baseline 24-hour urinary copper value more than 100 µg/day was in 66% (n=33) patients and more than 2 times of ULN (>80 µg/day) in all. With PCT, it increased to more than 5 times ULN (200 µg/day) in 100% of patients. Sixty percent (30) of patients were having >1000 µg/day and 20% (10) >1600 µg/day.

We started DP (mean dose of 20 mg/kg) in almost all patients along with zinc acetate (mean dose of 60 mg/kg/day). Symptoms managed accordingly. During the follow-up, monitoring was done for clinical and biochemical improvement, ensuring compliance and to identify adverse effect. Five patients showed poor response to therapy with no improvement in liver function tests despite of good compliance. Two patients develop Stevens Johnson syndrome (SJS), one develop renal failure with rising creatinine. Twenty-seven (54%) patients showed improvement on chelation therapy with fall in hepatic enzymes and improvement in neurological symptoms. In two patient penicillamine was stopped

Highlights

- Wilson's disease (WD) has considered as the common cause of metabolic liver disease in children above five years of age.
- Hospital based studies in India has reported WD to account for 7.6% and 19.7% of total patients of hepatobiliary disease.
- We reported the youngest patient presented at three years of age with acute hepatitis. Thus, age should be no bar to evaluate for WD.
- In this study, patient with hepatic WD has mean age at onset 7.5 years (delay in diagnosis of 7 months) and in neurological WD mean age was 10.5 years (delay of 12 months). All patients with neurological WD were more than 8 years except one was 4-year-old.
- The preferential standard treatment of WD is chelation therapy using D-penicillamine. Other drugs include trientene and zinc acetate. These drugs are highly efficient but have side effects so needs monitoring frequently.[36]

Table 1. *Clinical presentation*

Mode of presentation	Hepatic n=38/50 (76%)	Neuropsychiatric 12/50 (24%)	Others
Mean age	**7.5 years**	**10.5 years**	
Clinical forms (n)	Acute hepatitis (8) Acute liver failure (6) Chronic liver disease (24)	Choreoathetosis (10) Dystonic syndrome (9) Parkinson's syndrome (8) Neuroregression (8) Behaviour changes (7) Bulbar palsy (6) Tremors flapping (4) Cerebellar dysfunction (4) Abnormal Neuroimaging (8) Poor scholastic performance (7)	Both hepatic and neurological (4) Renal (1) Articular (2) Hemolytic anemia (2)

Table 2. *Clinical and biochemical profile of patients*

Jaundice	26 (52%)	Serum bilirubin mean (range) md/dL	4.2 (0.6-16)
Ascites with edema	20 (40%)	Serum albumin mean (range) gm/dL	2.9 (1.9-3.9)
Portal hypertension	17 (34%)	ALT mean (range) IU/L	158 (23-1848)
Variceal bleed	14 (28%)	AST mean (range) IU/L	216 (11-1708)
Coagulopathy not corrected with vitamin K	22 (44%)	PT INR mean (range)	2.44 (1.2-9)
Splenomegaly	20 (40%)	ALP mean (range) IU/L	240 (59-810)
Hepatomegaly	15 (30%)		

AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, ALP; Alkaline phosphatase, PT INR; Prothrombin time international normalized ratio

Table 3. *Comparison of hepatic form with neurological form of WD*

S no.	Characteristics	Hepatic (38)	Neurological (12)	p-value
1	Mean age at onset (years)	7.5	10.5	p=0.710
2	Cirrhosis	19	6	
	Micro nodular	13	6	p=0.303
	Macro nodular	6	0	
3	S.ceruloplasmin (mg/dL) (mean)	19	20.12	p=0.248
	<10	5	4	
4	24-hour urinary copper without challenge (mean)	170	208	p=0.769
	>100 µg	25	8	
5	24-hour urinary copper with challenge (µg) (mean)	1033	949	p=0.951
	>2 ULN	All	All	
	>1000 µg	8	3	p=0.911
	>1600 µg	4	2	
6	Ferenci score ≥4	30/38 (78.9%)	12 (100%)	p=0.200
7	KF ring positive	17/38 (44.7%)	10/12 (83.3%)	p=0.045
8	Mortality	7/38 (18.5%)	2/12 (16.6%)	p=0.769
9	Follow-up			
	Improving clinical symptoms	20	7	p=0.989
	Disappearance of KF ring	10	5	p=0.515

WD; Wilson's disease, ULN; Upper limit of normal, KF; Kayser Fleischer

after improvement and they were maintained on zinc acetate.

Overall, nine patients died during the study period, among which three patients were having acute hepatic failure, four were in decompensated chronic liver failure and two were having neurological WD.

Discussion

WD has considered as the common cause of metabolic liver disease in children above five years of age.[18,19] It account for 8-20% of cases with acute liver failure (ALF) similar to other etiologies.[17] The prevalence of WD in European population has reported between 10-30 per 100,000 and in Asian countries it is high and reported between 33 and 68 per 100,000.[6,7] In India, there are mainly hospital based studies with no community-based studies on epidemiology of WD. Hospital based studies in India has reported WD to account for 7.6% and 19.7 % of total patients of hepatobiliary disease.[19]

Clinical Features

Patients usually become symptomatic between 5-35 years with wide range. In previous studies, youngest asymptomatic patient reported was 4 months, old diagnosed on family screening and youngest symptomatic patients was 3-year-old.[20,21] We reported the youngest patient presented at three year of age with acute hepatitis. Thus, age should be no bar to evaluate for WD. Studies reported mean age at onset of clinical feature between 7.7 to 9.2 years with mean delay in diagnosis of about 1.5 to 3 years.[22] We also reported similar findings with onset of symptoms at mean age of 8.3 years with lag of 11 months to diagnosis.

Some studies had reported male predominance.[18,20] We reported the male: Female ratio of 2/1. However, some studies have shown, equal sex ratio[11] and others, few have shown female predominance.[21] Hence, there is no sex predilection for WD, although the clinical presentation of WD varies with age and gender.[22]

The younger children presented with mainly hepatic manifestations (<10 years: 83%; 10-18 years: 52% >18 years: 24%), while neurological presentations increases as age increases (<10 years: 17%; 10-18 years: 48%; >18 years: 74%).[19,22] Delay in the diagnosis of WD was more longer in neurological WD (18 months) as compared to hepatic WD (6 months).[20] In this study, patient with hepatic WD has mean age at onset 7.5 years (delay in diagnosis of 7 months) and in neurological WD mean age was 10.5 years (delay of 12 months). All patients with neurological WD were more than 8 years except one was 4-year-old.

Studies have shown that neurological features at diagnosis are more common in males and hepatic in females but in children, we did not observed such difference.

Manifestations in hepatic WD can vary from acute hepatitis to acute/fulminant hepatic failure, and there may be chronic hepatitis with compensated or decompensated cirrhosis.[23]

Neurological WD manifests as movement disorder like ataxia, dystonia, tremors or Parkinson's like an akinetic-rigid syndrome with or without bulbar involvement.[24]

Children mainly present with hepatic disease. In this study, hepatic manifestations were seen in 75% patients, neurological in 24% of patients. Studies from India reported isolated hepatic disease in 20-54% of pediatric patients, isolated neurological features in 8-22% of patients and combined neurohepatic disease in 11-36% with 15-35% of patients identified on family screening while asymptomatic.[19-21]

In this study, six patients presented with ALF with encephalopathy, eight with acute hepatitis (without encephalopathy). Rest patients presented with chronic liver disease. Studies have shown ALF constitutes 10 to 30 percent among all cases of WD, acute hepatitis 10 to 25 percent and chronic hepatitis in 10 to 30%. WD might be responsible for 9% of all ALF cases similar to other etiologies.[19,21,23,25]

Many patients with chronic liver disease had cirrhosis at the time of diagnosis. In this study, cirrhosis seen in 25 patients (50%) with majority having micronodular cirrhosis and portal hypertension was seen in 34%. Various studies reported cirrhosis in 30 to 60% patients.[19,21,23,25]

In our study, most common neurological presentation was movement disorder (90%) with dystonia, chorea athetosis, Parkinson's like presentation. Three patients also have seizures. Machado et al.[24] described dystonia in 69% of patients with neurologic presentations. A study from Bangalore reported Parkinsonism 62.3%, dystonia 35.4%, cerebellar 28%, pyramidal signs 16%, chorea 9%, athetosis 2.2%, myoclonus 3.4% and behavioural abnormalities 16% among various neurological features.[15] Deterioration of handwriting and school performance in older children, and dysarthria, and drooling of saliva in younger children may be the early neurological manifestations.[24,26]

Most patients with neurological WD had underlying hepatic involvement and 20-30% patients may have past history of jaundice.[19] In this study, most patients with neurological Wilson have normal liver function test but all have coarse echotexture of liver on ultrasonography and six were having micronodular cirrhosis. Neuroimaging was showing hyper-intensities in basal ganglia on T2 images in 8 patients, cerebral atrophy with gliosis in one. Nerve conduction study done in one patient showing pure motor axonal neuropathy affection. MRI features pathognomonic of WD are "face of giant panda" (14.3%), tectal plate hyperintensity (75%), central pontine myelinolysis-like abnormalities (62.5%), and concurrent signal changes in basal ganglia, thalamus, and brainstem (55.3%).[27]

Some other manifestations had been reported in literature like gigantism, renal abnormalities (8-10%) such as aminoaciduria, nephrolithiasis, hypercalciuria and nephrocalcinosis, coomb negative hemolytic anemia (7%) cardiomyopathy, myopathy, bone and joint manifestations, hypoparathyroidism, and pancreatitis.[19]

In this study, two patients present with direct Coombs test negative hemolytic anemia, one patient develops hydronephrosis with renal calculi. Osseo muscular symptoms may rarely be the presenting feature.[19,28] Our two patients presented with arthritis of knee with effusion. Investigations reveal chronic liver disease and WD was diagnosed later on.

In this study, KF ring are present in 44.7% of hepatic WD and 83.3% of neurological WD. Presence of KF ring is highly specific for WD. Studies had shown KF ring are always bilateral and seen in 50 to 60% of hepatic and 95 to 100% cases of neurological WD.[29] Younger patient may not develop KF ring at time of diagnosis. We have only two patients younger than 6 years with positive KF ring on slit lamp examination. KF ring may also present in other diseases also such as biliary cirrhosis, cryptogenic cirrhosis, chronic active hepatitis, and neonatal hepatitis.[19]

Two patients were having sunflower cataract. Copper deposition in the anterior capsule of lens lead to sunflower cataract in 2-17% of patients.[30] Night blindness, exotropic strabismus, optic neuritis, and optic disc pallor are rarer ophthalmological manifestations.[29,30]

Diagnosis

There is delay in diagnosis of WD due to variable clinical presentation. In addition there is no single reliable test easily available for diagnosing WD. After suspecting WD clinically, a wide range of test may be required to confirm the diagnosis. Over-reliance on specific test delays the treatment and leads to progression of disease.

The modified Leipzig scoring system incorporating routinely available laboratory tests has 98.1% sensitivity and 96.6% specificity for diagnosing WD.[16,19] In this study, we had use combination of various test for diagnoses of WD.

Serum Ceruloplasmin

Serum ceruloplasmin levels less than 20 mg/dL are seen in WD with values lower 10 mg/dL are highly suggestive. This test is use for patient more than 1 year of age. Values between 10-20 mg/dL are seen 20% of in heterozygotes.[19] However, levels are falsely elevated in presence of acute inflammation and low normal values are seen in 50% of patients with acute liver disease.[33] Upto 40% of patients with hepatic and 15% of neurologic WD have normal levels.[32] Serum ceruloplasmin is typically lower in neuropsychiatric disease compared with liver disease. Studies have shown that low serum ceruloplasmin has sensitivity of 21-56% and specificity of 63-84% for diagnosis WD in presence of hepatic disease.[32]

In this study, mean serum ceruloplasmin level was lower in neurological WD (18 mg/dL) than hepatic (25 mg/dL) WD. All patients with neurological WD were having serum ceruloplasmin level less than 20 mg/dL but with hepatic WD 32% were having serum ceruloplasmin values in normal range. Most of them have acute hepatitis.

24-hour Urinary Copper Assay

Level of more than 100 mcg/24-hour are diagnostic for symptomatic WD.[31,33] For asymptomatic patients lower value of cut off levels of 40 mcg/24-hour increases the sensitivity of test.[19,31] Our all patients have values more than 2 times of upper limit of normal. PCT had been consider useful in past but now it is not recommended because of high false positive results.[34] This test should be perform in equivocal cases only.

Hepatic Enzymes

Previous studies reported that low level of serum alkaline phosphatase (ALP) with low ALP to serum bilirubin ratio or high value of aspartate aminotransferase as compared to ALT should also raise suspicion of WD. A ratio of more than 2.2 between AST and ALT may have a sensitivity of 94% and a specificity of 86% for WD.

However, these findings are not seen in all cases.[32,33,35] We observed AST to ALT ratio more than 2 in eleven patients.

Treatment and Follow-up

The preferential standard treatment of WD is chelation therapy using DP. Other drugs include trientene and zinc acetate. These drugs are highly efficient but have side effects so needs monitoring frequently.[36]

In neurological WD, there may paradoxical deterioration of symptoms after starting DP. Studies had reported an incidence of 10% for such deterioration but one study by Brewer et al.[36,37] reported it as high as 50%. In our study one patient with neurological WD, develop mild neurological deterioration with increasing dose of penicillamine after 1 year of good improvement. Therefore, we must start DP at the lowest possible dose in neurological WD. The dose is slowly increase with regular clinical and biochemical monitoring. Significant other adverse effects reported in 10-30% of patients on DP therapy.[19]

Our two patients develop SJS, one develop renal failure with rising creatinine. The drug should stop immediately, if early hypersensitivity reactions occur. Clinical improvement in hepatic WD in response to chelation therapy is shown by decreasing level of jaundice, ascites, and portal hypertension. Studies had shown clinical response to treatment of around 90% in hepatic and 55% in neurological disease.[19] In our study after follow-up of 3 years, 27 patients showed clinical improvement on chelation therapy.

Reappearance or appearance of KF ring in whom it was absent should suspect the possibility of non-compliance of drugs or failure of therapy. Fulminant hepatic failure has 100% mortality in absence of liver transplantation.[38] We noticed 20 percent mortality in hepatic WD and 18 percent mortality in neurological WD. Overall, nine patient died during the study period, among which three patients were having acute hepatic failure, four were in decompensated chronic liver failure and two were having neurological WD.

Conclusion

Children with WD may present with varied and unusual clinical manifestation. Therefore, early suspicion and prompt diagnosis is necessary for good prognosis. Family screening should be performed for every diagnosed patient. It requires wide range of tests as genetic testing is not easily available. Acute liver failure has high mortality. Early chelation therapy reverses the clinical and biochemical abnormalities.

Acknowledgement

We would like to express our gratitude to our teachers and mentors Late Professor Dr. RK Gupta, and Dr. ML Gupta who guided us to do this study.

Ethics Committee Approval: Office of the Ethics Committee Sawai Man Singh Medical College and Attached Hospitals, Jaipur (decision no: 814, date: 26.08.2021) approved the study.

Informed Consent: Patients visiting the outpatient department or admitting in wards with clinical presentation suggestive of WD were enrolled in the study after obtaining a valid informed written consent.

Author Contributions: Vajpayee S: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Goyal AK: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Yadav Y: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Agarwal R: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation.

Conflict of Interest: The authors declare no conflicts of interest. The authors are responsible for the content and writing of this article.

Financial Disclosure: The authors have no conflicts of interest to declare.

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Journal of Pediatric Academy

Case Report

Year: 2024 Volume: 5 Issue: 2
Doi: 10.4274/jpea.2024.275
J Pediatr Acad 2024; 5: 70-72

Moyamoya Disease Masquerading as Hemiplegic Migraine in a Child: A Case Report from India

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Article Information

Article Type: Case Report
Article Group: Pediatric Neurology

Received: 29.11.2023
Accepted: 30.04.2024
Epub: 09.05.2024
Available Online: 01.07.2024

Cite this article as: *Kumar K, Kumar D, Mathur SB. Moyamoya Disease Masquerading as Hemiplegic Migraine in a Child: A Case Report from India. J Pediatr Acad. 2024; 5: 70-72*

Abstract

Moyamoya disease (MMD) is a chronic progressive steno-occlusive disease of the intracranial arterial vessels and their branches characterized by puff smoke appearance on angiography. Multifocal neurological insults and deficits are commonly observed in children with MMD. A 7-year-old boy presented with multiple episodes of transient hemiparesis preceded by headache, vomiting, and visual auras was initially labeled as sporadic hemiplegic migraine according to the International Headache Society criteria. However, the rare association of hemiplegic migraine with MMD compelled us to perform magnetic resonance imaging and digital subtraction angiography, which revealed MMD as the underlying cause for the alternating hemiplegia and headaches in the child.

Keywords: Moyamoya disease, alternating hemiplegia, hemiplegic migraine

Introduction

Moyamoya disease (MMD) is an infrequent disorder affecting the blood vessels in the brain and is characterized by narrowing of the distal internal carotid arteries (ICAs) and their branches. This narrowing progressively occludes the arteries in the circle of Willis, leading to the development of distinctive collateral vessels, which appear like a puff of smoke on angiography.[1] The average annual incidence of this condition is 0.54 per 100,000 populations and is prevalent among pediatric patients in Eastern Asia.[2]

Headache associated with MMD is a well-known presentation that persists even after revascularization surgery.[3] Although very few, there are reports stating that differential diagnosis of MMD should always be made in patients presenting with migraine-like headaches and alternating neuro deficits.[4-6] Here, we present an unusual case of MMD where the primary manifestation was alternating hemiplegic migraine.

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A 7-year-old boy presented to a pediatric emergency department with the complaint of sudden onset weakness in the right side of the body and deviation of the mouth toward the left side. The event was preceded by auras consisting of headache, vomiting, bright sparkling lights in front of his

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eyes, and a sudden urge to urinate. The headache was throbbing and pulsatile in nature, of variable intensity, and resolved after a few hours, but focal neurological deficits continued to persist. On reviewing the history, there were three such episodes of left-sided body weakness preceded by aura in the past 9 months, which resolved within 6 h without any residual focal neurological deficits. Examination revealed: Glasgow coma score, 15/15; heart rate, 94; respiratory rate, 26; pulse, normovolemic and regular; blood pressure, 104 systolic and 78 diastolic; CFT, less than 2 s; fundus, no abnormality; there were no cranial nerve deficits; and right-sided hemiparesis was present (power of 2/5 by Medical Research Council scale). The rest of the neurological and systemic examinations were unremarkable. Family history was negative for epilepsy, migraine, or any psychiatric disorder. Clinically, the child was labeled sporadic hemiplegic migraine as per the International Headache Society criteria.

Hematological parameters: hemoglobin, 11 g/dL; total leukocyte count, 8,800; platelets, 2.8 lac/cumm; ESR, 10 mm; other vasculitis markers (ANA, anti-ds-DNA, C-ANCA, P-ANCA) were unremarkable; biochemical parameters: serum sodium, 142 mmol/L; serum potassium, 3.8 mmol/L; serum dextrose and ionized calcium, 80 mg/dL and 0.99 mmol/L, respectively. Arterial blood gas and urine drug/toxin screening were normal. Both electrocardiography and electroencephalography were normal for age. However, magnetic resonance imaging (MRI) brain with angiography showed acute to subacute infarction in the left parieto-occipital region with non-vascularization of bilateral ICA distal to the origin of ophthalmic arteries with filling defect in bilateral anterior cerebral artery and left middle cerebral artery through multiple lenticulostriate and thalamostriate collaterals, features suggestive of MMD, stage 3 (Suzuki classification) (**Figure 1 and 2**). Other investigations were ordered to rule out organic causes of headache with hemiplegia, i.e., mitochondrial disorder-MELAS, transient ischemic attack (TIA), and intracranial arteriovenous malformations. Subsequently, over the next 24 h, right-sided hemiparesis improved with power improvement from 2/5 to 4/5, with complete resolution of right-sided facial nerve deficit. Consent from both parents was obtained before the inclusion of the child for reporting the case, in accordance with the institutional ethics guidelines.

Discussion

Hemiplegic migraine is an unusual form of migraine with aura where the headache is accompanied by one-sided weakness that switches sides during or between attacks as well as visual auras. It can either run in families (familial hemiplegic migraine) or occur sporadically in an individual (sporadic hemiplegic migraine).[7,8]

In our case, the clinical presentation met the diagnostic criteria for sporadic hemiplegic migraine, characterized by reversible motor weakness and visual-sensory auras, as defined by the international classification of headache disorders (ICHD-3).[9] To rule out other potential causes that could mimic migraine, neuroimaging was performed, revealing MMD as the underlying condition.

MMD is a progressive narrowing and eventual blockage of blood vessels in the brain. The symptoms vary depending on the age of onset, with headaches, seizures, TIAs, and ischemic strokes being more common in childhood, whereas subarachnoid and intracerebral hemorrhages occur more frequently in adulthood.[10] Although headache and aura as the initial symptoms of pediatric MMD are rare, only a few case reports have described such occurrences.

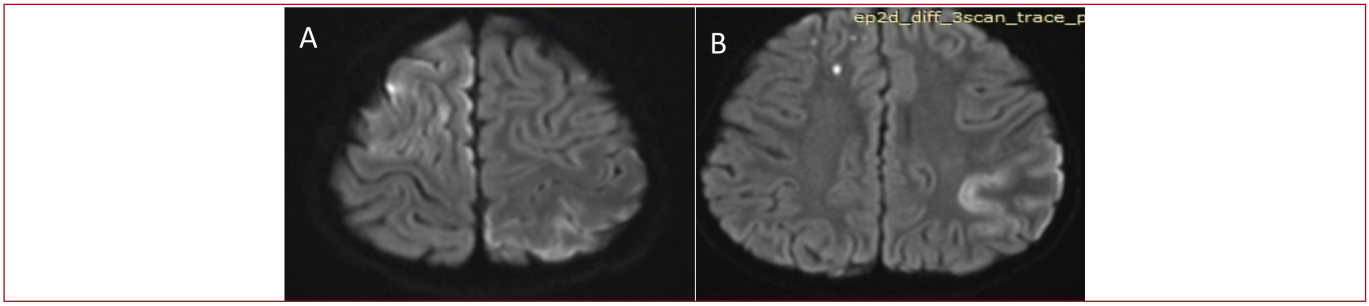

Figure 1. MRI Images (A,B) shows acute to subacute non-territorial infarct involving right frontal and left parieto-occipital region.
MRI; Magnetic resonance imaging

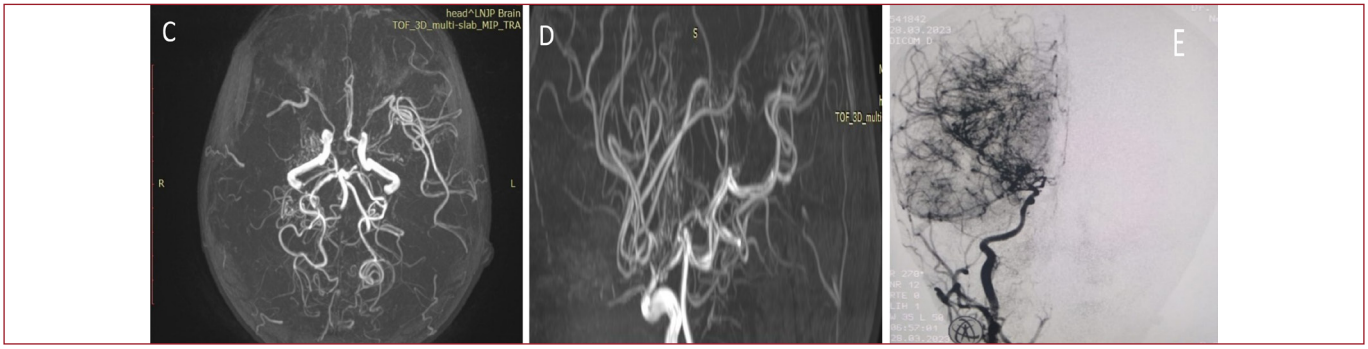

Figure 2. MRI brain (C,D) shows non-visualisation of B/L ICA distal to the origin of ophthalmic arteries with multiple collaterals of lenticulostriate and thalamostriate arteries (E) giving puff of smoke appearance.
MRI; Magnetic resonance imaging, ICA; Internal carotid artery

The first such occurrence was described by Bernstein[11] in 1993 in a 6-year-old girl. Cerebral artery nociceptor likely play a role in generating headaches in MMD, as studies have shown that stretch on these vessels can produce nausea and referred pain in regions associated with migraine attacks.[12] Neuroimaging techniques like computed tomography and MRI are useful in identifying organic or vascular causes in these patients, but cerebral digital subtraction angiography (DSA) remains the gold standard for diagnosing and monitoring MMD. DSA reveals classical angiographic changes, such as progressive stenosis and occlusion of the supraclinoidal part of the ICAs (usually bilateral) and the characteristic appearance of collateral vessels resembling a “puff of smoke”.

Conclusion

In conclusion, headaches associated with MMD can manifest as migraine with or without auras and may be the first and only presenting symptom. A high level of suspicion, consideration of various differential diagnoses, and early neurovascular imaging are crucial for diagnosis and prompt initiation of treatment.

Informed Consent: Consent from both parents was obtained before the inclusion of the child for reporting the case, in accordance with the institutional ethics guidelines.

Author Contributions: Kumar K: Concept, Data Collection or Processing, Literature Search, Writing.; Kumar D: Design, Analysis or Interpretation, Writing.; Mathur SB: Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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Journal of Pediatric Academy

Case Report

Year: 2024 Volume: 5 Issue: 2
Doi: 10.4274/jpea.2024.258
J Pediatr Acad 2024; 5: 73-75

MRI Evaluation of Vasculopathy and Additional Intracranial Manifestations in Morning Glory Disc Anomaly

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Article Information

Article Type: Case Report
Article Group: Pediatric Neuroimaging Group Study

Received: 03.10.2023
Accepted: 12.03.2024
Epub: 30.04.2024
Available Online: 01.07.2024

Cite this article as: *Heller GD, Kumar MS. MRI Evaluation of Vasculopathy and Additional Intracranial Manifestations in Morning Glory Disc Anomaly. J Pediatr Acad. 2024; 5: 73-75*

Abstract

Morning glory disc anomaly (MGDA) is rare, but its fundoscopic findings are well documented in the ophthalmologic literature. It is sporadic, without sexual predisposition, and usually unilateral. Furthermore, it is associated with numerous central nervous system anomalies, including vasculopathy. This case series reports four pediatric patients over a 3-year period in whom ophthalmologic evaluation identified MGDA. Magnetic resonance imaging and magnetic resonance angiography were subsequently performed to assess for associated intracranial vascular anomalies. This report is of significance because it demonstrates the spectrum of intracranial vasculopathy in this rare entity.

Keywords: Morning glory disc anomaly, intracranial vasculopathy, pediatrics

Introduction

Morning glory disc anomaly (MGDA) is a rare, sporadic entity without sexual predisposition and is associated with distinct ocular and intracranial manifestations.[1-11] Its enlarged optic disc opening is thought to represent the sequelae of defective embryonic fissure closure or a developmentally enlarged optic stalk[9] and is named after its fundoscopic resemblance to the morning glory flower. Fundoscopic evaluation demonstrates radially oriented thin vessels emanating toward the periphery of the retina.[1,9] Intracranial manifestations are ipsilateral with respect to ocular findings.[1-11] Enlargement of the ipsilateral optic nerve can be present; this may represent an optic pathway tumor.[1-3, 6,11] Intracranial magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) performed following the diagnosis of morning glory anomaly can reveal a spectrum of intracranial anomalies, which can range from normal intracranial morphology to multiple severe anomalies, including corpus dysgenesis of the corpus callosum, Chiari 1 malformations, sphenoid meningocoele, and vasculopathy with or without a Moya Moya pattern.[1-11]

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We report four cases that demonstrate the spectrum of neuroradiologic findings in MGDA, with specific attention to vasculopathy of Willis's circle.

A retrospective chart review from 2000 to 2020 yielded four patients diagnosed with morning glory anomaly. The submission was approved by the Institutional Review Board of the Mount Sinai School of Medicine in accordance with Mount Sinai's Federal Wide Assurances.

Case Reports

Patient 1: A 3-month-old female was diagnosed with morning glory anomaly OD on ophthalmologic evaluation by a neuro-ophthalmologist. MRI subsequently performed demonstrated normal ocular globe morphology without intracranial manifestations. Imaging is not included (**Figure 1a, b**).

Patient 2: A 6-year-old male presented with decreased visual acuity OS. Ophthalmologic evaluation revealed morning glory syndrome. MRI demonstrated left globe dysplasia without any additional brain anomaly. MRA demonstrated stenosis of the distal left internal carotid artery without the Moya Moya pattern (**Figure 2a-c**).

Patient 3: Eight-month-old male with morning glory OD and posterior ocular globe defect appreciated on MR. MRA revealed stenosis of the right distal internal carotid artery with a Moya Moya pattern of collateralization.

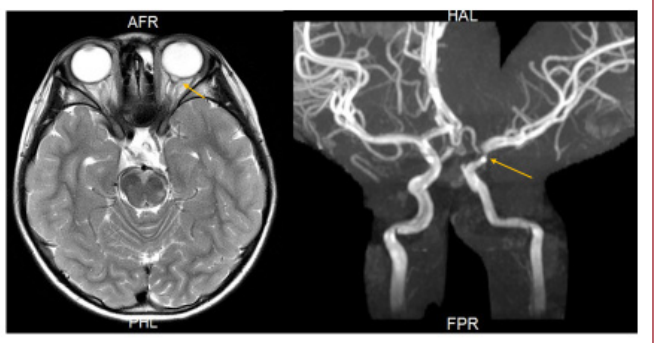

Figure 1a Figure 1b

Figure 1. a. Axial T2 weighted image reveals a defect in the left posterior globe at the optic disc insertion (arrow). **b.** Magnetic resonance angiography demonstrates stenosis of the distal left internal carotid artery (arrow).

Patient 4: An 11-month-old female diagnosed with bilateral morning glory anomaly and enlargement of the intraorbital portions of both optic nerves. Inversion recovery imaging of the nerves demonstrated abnormal signals (not shown), and post-gadolinium images demonstrated enlargement and irregular enhancement of both optic nerves compatible with optic nerve glioma. Sagittal T2-weighted imaging demonstrates sphenoid meningocoele. MRA of the cerebral vasculature demonstrates bilateral distal internal carotid artery stenosis with extension into the M1 segments of the middle cerebral arteries. MRA also demonstrates a Moya Moya pattern with collateralization and significant stenosis of the left posterior cerebral artery (not shown) (**Figure 3a-d**).

Results

This report presents four patients with a diagnosis of MGDA and associated MRI. One patient presented without intraorbital or intracranial abnormalities on MR evaluation. The second patient presented with MGDA with left ocular globe anomaly on MRI as well as stenosis of the distal left internal carotid artery without Moya Moya pattern on MRA. Two patients demonstrated ocular findings and intracranial vascular stenosis with collateralization effort compatible with the Moya Moya pattern. One of these patients was also diagnosed with a sphenoid meningocoele and neurofibromatosis type 1. Although usually unilateral, the fourth patient was diagnosed with a bilateral anomaly.

Discussion

MGDA is a rare congenital syndrome without sexual predisposition. It is usually unilateral although it can be bilateral, as in the fourth submitted case.[10] Fundoscopic findings of MGDA are well documented in the ophthalmology literature.[1-11] MGDAs may present with enlargement of the optic nerve, and neoplasms can be suspected, such as optic pathway gliomas in neurofibromatosis type 1, as demonstrated in the fourth patient.[1-4,6,11]

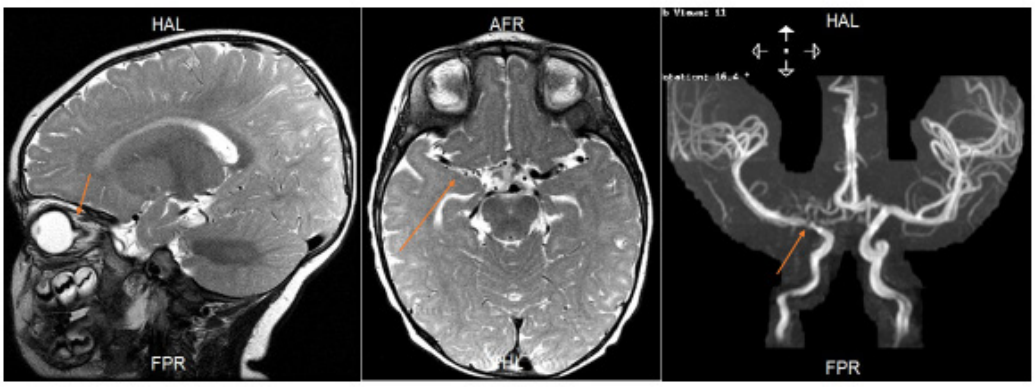

Figure 2a Figure 2b Figure 2c

Figure 2. a. Sagittal T2 weighted image demonstrated a defect in the right posterior globe (arrow). **b-c.** Axial T2 weighted and MR Angiographic images demonstrated collateral vasculature at the level of the distal right internal carotid artery stenosis (arrows).

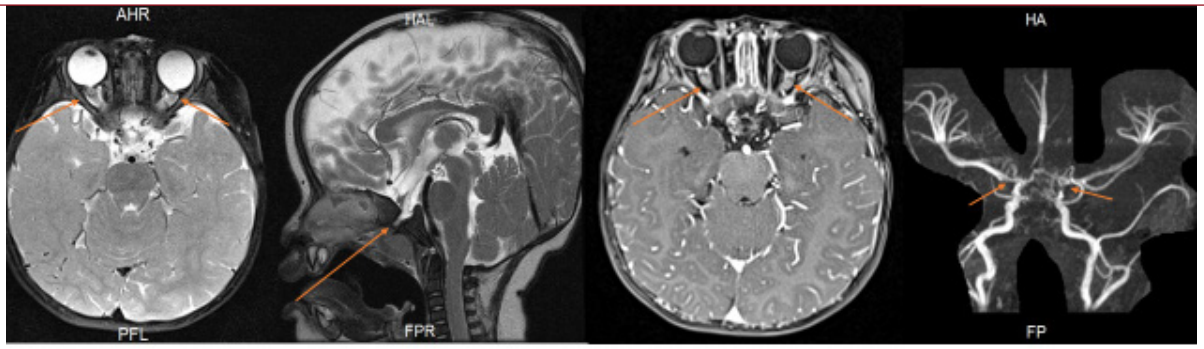

Figure 3. a. Axial T2 fat saturated image demonstrates bilateral ocular defects at the optic disc insertion level (arrow). **b.** Sagittal T2 weighted image demonstrates a sphenoid meningocoele (arrow). **c.** Axial post gadolinium images reveal enlargement and patchy enhancement of both intraorbital optic neves (arrow). **d.** Magnetic resonance angiography reveals bilateral distal Internal Carotid Artery stenosis with Moya Moya pattern (arrow).

Morning glory anomaly is associated with midline defects, such as dysgenesis of the corpus callosum, Chiari 1 malformations, sphenoid meningocoele, and intracranial vasculopathy, such as distal integral carotid artery stenosis and Moya Moya collateralization effort.[5,6,8] Pituitary dysfunction is also established, presumably related to basal cephalocoele development.[7,9]

There are multiple associated intracranial anomalies in morning glory anomaly.[1-11] As a result, when morning glory anomaly is detected, neuroimaging is of value in the patient's clinical assessment.

In summary, this case series demonstrates the constellation of intracranial manifestations of morning glory anomaly with specific emphasis on multiple patterns of intracranial vasculopathy. Therefore, neuroimaging is an important component of evaluation for this condition.

Informed Consent: Retrospectively study.

Author Contributions: Heller GD: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Kumar MS: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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