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Recurrent otitis media and iron deficiency anemia in autism

Heba Tallah Sherif Abd El Hady and Ghada Tarek Orabi

Department of Research on Children with Special Needs, Medical Research and Clinical Studies Institute, National Research Centre, Cairo, Egypt

Correspondance to: Heba Tallah Sherif Abd El Hady (MD)
Department of research on children with special needs, Medical Research and Clinical studies Institute, National research centre.
El-Behowth St., PO Box 12311,
Dokki, Cairo, Egypt.
Telephone: +201222402003
Postal code: 11865.
Email: hebasherif2008@live.com

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Background
Acute otitis media (AOM) is common in children and may become recurrent (ROM) or chronic if untreated. Children with autism spectrum disorder (ASD) have a higher incidence of otitis media, but diagnosis is often delayed due to communication challenges. Iron deficiency anemia (IDA), prevalent among ASD children, impairs immune function and may increase the risk of recurrent infections.
Objective
This study aims to evaluate the association between IDA and ROM in ASD children, hypothesizing that IDA increases the risk of ROM in this vulnerable group.
Materials and methods
A complete blood count and serum ferritin levels were assessed in 70 autistic children diagnosed with recurrent otitis media by history taking, otoscopic and tympanometry examination. Iron deficiency anemia was found to be statistically significant with recurrent otitis media.
Results and conclusion
In those 70 autistic children, children with recurrent otitis media (ROM) exhibited significantly lower hemoglobin levels, more severe anemia, lower mean hematocrit value (MCV), and Mean Corpuscular Hemoglobin (MCH) compared to autistic children without ROM. These findings suggest that ROM is associated with more apparent hematological alterations, possibly due to chronic inflammation or nutritional deficiencies.
According to the results, iron deficiency anemia may be a risk factor for this prevalent illness in infancy and childhood and raises the likelihood that autistic children may experience recurrent episodes of ear infections. Therefore, it is recommended that every autistic child, diagnosed with acute otitis media episodes, have their hemoglobin level assessed. Also, Iron deficiency anemia correction is a successful supplementary therapeutic option for reducing otitis media recurrence.

Keywords: Autism, hemoglobin, iron deficiency anemia, otitis media.

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Introduction

One of the most common inflammatory conditions in children is acute otitis media (AOM) [1]. Otitis media is typically inflammation of the middle ear and is considered recurrent (ROM) when three or more attacks of acute otitis media, occur in a six-month duration or more in a year, with periods of complete remission in between [2]. Chronic Suppurative Otitis Media (CSOM) is a persistent ear infection described by ongoing drainage of pus from the middle ear. This condition can result from untreated acute otitis media or recurrent ear infections. Mastoiditis, diminution of hearing, tympanic membrane perforation, chronic ear infection, cholesteatoma and labyrinthitis can all result from the middle ear infection's extension or persistence [3].

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that leads to significant social impairment (ASD), characterized by excessively restricted, and repetitive behavior with limited interests, as well as social and communication difficulties. ASD is thought to affect 1% to 2% of people globally, is at least 2-3 times more frequent in males, and is typically diagnosed in the first few years of life [4]. Children with ASD should have a thorough history as well as

physical and audiological examination, just like any other kid with language impairments [5]. Some studies reported the incidence of middle ear infections was higher among children with ASD than their typically developing peers. Adams and colleagues in 2016 reported a higher incidence of otitis media and its related complications as effusion, otorrhea, and mastoiditis than in typically developing children. Findings from research depending on parental reports of prior ear infections also suggest a higher incidence of Otitis media among ASD children than their counterparts [6]. However, reaching a diagnosis in Children with ASD could be very challenging, due to their hypersensitivity to auditory stimuli, and their communication deficits, as they may need sedation to complete behavioral audiometry and middle ear exams [7]. Making it more difficult to reach an early diagnosis. As a result, undiagnosed and untreated children with ASD engage in maladaptive behaviors like anger and self-harm, which might conceal the unpleasant symptoms of underlying conditions like AOM [8,9]. Often, these behaviors are mistaken as part of the behavioral manifestations of the autism spectrum disorder, resulting in missed or delayed diagnosis of otitis media and its associated problems. Therefore, early identification of ear infections, their potential risks, and correlative or contributing factors is crucial to reach an early and proper diagnosis in this group. Several studies have linked iron deficiency anemia to suppurative otitis media and acute otitis media with effusion [10,11].

Anemia is the decrease in hemoglobin concentration brought on by a lower red cell count than age-matched control values. In children aged 6 to 48 months, the normal hemoglobin concentration is 12.0 g/dL on average (range: 10.5 to 14.0). Iron deficiency is the primary cause of childhood anemia, and iron deficiency anemia (IDA) is highly prevalent in underdeveloped nations and is linked to low socioeconomic level [12]. The correlation between iron deficiency anemia and otitis media has been attributed to changes in the immune system that lead to lower immune functions. Iron deficiency is associated with two different immune system changes: a decreased T cell lymphocyte response to pathogenic pathogens and a decreased neutrophil bactericidal activity. Severe infections are more common in children with moderate to severe iron deficiency anemia than in those without [6].

Iron deficiency anemia has also been linked to ASD. Estimates of iron deficiency anemia among children with ASD are around 28% [12]. Research has suggested altered iron and hemoglobin levels in children with ASD [13] and [14]. A study by Guns and colleagues in 2017 found that children with ASD had lower hemoglobin, iron, hematocrit and MCV than their typically developing peers, though these levels weren't low enough to establish a diagnosis of anemia, lower levels of hemoglobin and iron in ASD correlated with lower intellectual abilities and memory. Lower levels of hemoglobin and iron among children with autism could be due to their restrictive eating behaviors and picky eating habits [13]. It is recommended to have their blood iron levels monitored routinely in their regular investigations.

Altered and lower blood iron levels are commonly observed in children with autism, which is a contributing factor to higher levels of middle ear infections. Therefore, these children possess a possibly higher risk of developing recurrent otitis media than their peers. Adding to the burden of being more at risk of developing such recurrent infection, is that diagnosis of recurrent otitis media (ROM) is commonly missed in them [5]. The current study investigates the potential relation between recurrent otitis media (ROM) in children with autism and Iron deficiency anemia (IDA) There is not enough literature on the effect of IDAon ROM in this vulnerable population.

We aim to evaluate the association between IDA and ROM in ASD Children.We hypothesized that ASD children with IDA would be at increased risk ROM.

Materials and methods

Sample size

A pilot study was done to detect the average level of serum iron in autistic children with and without otitis media, as there is currently no data available on those differences. Based on the results of that study, comparing the average level of some micronutrients in autistic children with and without otitis media with a ratio 1:1, and medium effect size (0.69). We need to study 21 autistic children with otitis media, 21 autistic children without otitis media, it was compensated by 15% due to the use of nonparametric tests, and compensated by 35% for possible losses so final sample size was 35 for each group of autistic children with and without otitis media to be able to reject the null speculated that the population means serum level of some micronutrients in both autistic children with otitis media compared to autistic children without otitis media are equal with probability (power) 0.95. The test of this null hypothesis has a Type I error probability of 0.05. The G power software was used to determine the sample size [12].

Subjects and methods

The current study was completed in audio-vestibular clinic, Medical Research Centre, National Research Centre. Cairo, Egypt. The study

had seventy participants. They were divided into the following two groups: 35 autistic children without OM with ages ranging between 6 and 10. They were divided into two study groups. Study group 1 contained 35 autistic children with ROM, and group 2 contained 35 autistic children without ROM. Inclusion criteria were children with an established diagnosis of autism based on the DSMV latest criteria, whereas exclusion criteria were children with fragile X, autism linked to syndromes, children with a history of food or medication allergies, other known neurological and mental conditions, or iron supplements.

The following protocol of assessment was carried out on all participants:

Tympanometry (to assess middle ear function and OM), medical history collection, and audiological tests, including otologic examinations with otoscopy, were all part of the thorough evaluation process for the children in the study.

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for ASD were used for diagnosis and severity evaluation [15], and the degree and severity of ASD symptoms were assessed using the Childhood Autism Rating Scale-2 (CARS-2 scale). When diagnosing ASD, a score of 30 was regarded as the cut-off rate. Mild to moderate degrees of autism was categorized by scores between 30 and 36.5, while severe autism was categorized by scores between 37 and 60 [16].

Lab investigations included serum iron; complete blood count (CBC)(hemoglobin concentrations, MCV, and MCH).

Peripheral venous blood samples for complete blood count and serum ferritin levels from all patients were taken. CBC was done by Automated hematology analyzers and normal Hb cutoff levels according to The World Health Organization 2024 (WHO) in children aged 5-11 years was $\geq$ 11.5 gm% [17].

Ethical issue: Ethical acceptance was provided by the ethical research committee of the National Nutrition Institute with approval number IN000167. All parents of children signed written consent after knowing all details about the study's nature and aim.

Statistical analysis

To organize, analyze, and create graphs, we used RStudio software version 4.4.1. We summarized numerical data using averages, standard deviations, medians, and interquartile ranges when appropriate. For categorical data, we employed numbers and percentages. Figures and percentages were utilized to estimate frequency. We assessed the normality of numerical data using the Shapiro-Wilk test and the Kolmogorov-Smirnov test. When comparing independent groups with respect to categorical data, we applied either chi-square tests or Fisher's exact tests, as appropriate, using the category of instances without otitis media as the reference level.

The student's t-test was applied to compare the two groups for regularly distributed numerical data, while the Mann-Whitney test was applied for comparing the two groups for non-normally distributed numbers. The limit for statistical significance was set at $P < 0.05$.

Results and discussions

The study was conducted on 70 participants, who were split into two groups, each consisting of 35 children. The first group of children with ASD didn't have otitis media and the second group was children with ASD that had otitis media. Our results showed that the demographic distribution was of an equal split between the two groups with and without otitis media, with males constituting 70% of the participants. The median age group was 7.5 years (age ranged from 6_10) (Table 1). There was no difference in age, or gender between the two groups as shown in (Table 2). The results showed that children with OM mostly suffered from anemia. there were 33 cases with moderate anemia, 2 cases with mild anemia, and no cases without anemia. Results regarding children without OM, there were 15 cases without anemia, 15 cases with mild anemia and 5 cases with moderate anemia (Fig. 1). Regarding the hemoglobin (Hb) Levels, children with OM had significantly lower Hb levels (10.23 ± 0.52) compared to those without OM (11.35 ± 0.37, $p < 0.001$). A higher percentage of children with OM had moderate anemia (94.3%) compared to those without OM (14.3%). In contrast, 42.9% of children without OM have no anemia, while none in the OM group were anemia-free (Table 3).

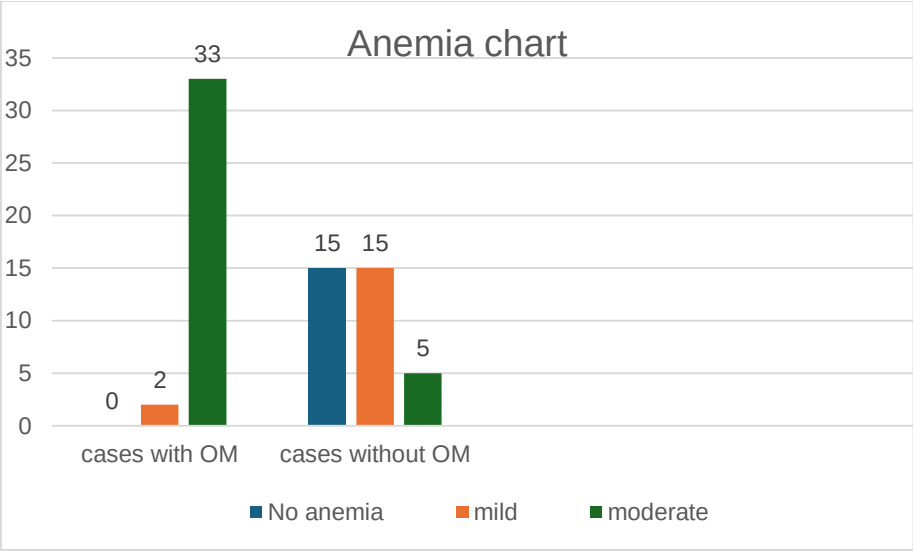

Fig. 1. Comparison of anemia severity between cases with OM and cases without OM.

Table 1 Demographic distribution of all studied group

Clinical data		**Children (n=70)**
Children (%)	Cases with OM	35 (50%)
	Cases without OM	35 (50%)
Gender (%)	Female	21 (30%)
	Male	49 (70%)
Age (years)		7.5 (6-9Y)

Data are expressed as n (%), and median (IQR).

Table 2 Demographic data of autistic children with and without otitis media

Demographic data	**Cases with OM (n = 35)**	**Cases without OM (n = 35)**	***P***
Age at diagnosis (years) (mean)	7 (6- 8.5)	8 (6- 9)	0.664
Gender			
Female	12 (34.3)	9 (25.7)	0.602
Male	23 (65.7)	26 (74.3)	

Data are expressed as n (%), and median (IQR).

Table 3 Hemoglobin and red cell indices in autistic children with and without otitis media

	Level	Cases with OM (n =35)	Cases without OM (n =35)	P
Hb (SD)		10.23 (0.52)	11.35 (0.37)	<0.001*
Hb (%)	Mild anemia	2 (5.7%)	15 (42.9%)	<0.001*
	Moderate anemia	33 (94.3%)	5 (14.3%)	
	No anemia	0 (0.0)	15 (42.9%)	
MCV (SD)		77.89 (1.95%)	79.48 (2.40%)	0.003*
MCV (%)	Microcytic	33 (94.3%)	29 (82.9%)	0.26
	Normocytic	2 (5.7%)	6 (17.1%)	
MCH (SD)		26.10 [25.7%]	27.50 [26.8%]	<0.001*
MCH (%)	Hypochromic	31 (88.6%)	10 (28.6%)	<0.001*
	Normochromic	4 (11.4%)	25 (71.4%)	
S.iron [mg/dl]		42 ± 0.35	77.65 ± 5.44	<0.001*
S.iron (%)	Iron deficieny	33 (94.3%)	10 (28.8%)	<0.001*
	Normal iron	2 (5.7%)	25 (71.4%)	

Data are expressed as n (%), mean (SD), and median (IQR). *:significant atP<0.05.

The Mean Corpuscular Volume (MCV) was slightly lower in children with OM (77.89 ± 1.95) than in those without OM (79.48 ± 2.40, p = 0.003). Most of both groups had microcytic anemia (94.3% in OM vs. 82.9% in non-OM), but this difference was not statistically significant (p = 0.26).

The Mean Corpuscular Hemoglobin (MCH) values were lower significantly in the OM group (26.10) than in the non-OM group (27.50, p < 0.001). A significantly higher proportion of children with OM have hypochromic RBCs (88.6%) compared to the non-OM group (28.6%, p < 0.001).

Regarding the serum Iron Levels OM cases have significantly lower serum iron levels (42 ± 0.36 vs. 77.66 ± 5.45, p < 0.001). Iron deficiency was much more prevalent in cases with OM vs cases without OM (94.3% vs. 28.8%). Cases with OM show a strong association with lower Hb, lower serum iron, and a higher prevalence of microcytic hypochromic anemia. The results demonstrated that children with autism and OM exhibited significantly lower hemoglobin levels, more severe anemia, lower MCV and MCH compared to autistic children without OM.

For many years, it has been proven that infection, diet, and health are closely linked. The immune system cannot operate properly without adequate consumption of vitamins and minerals. Middle ear disorders may be influenced by nutritional variables [18].

People with ASD frequently suffer from chronic and recurrent otitis media, auditory processing abnormalities such as central auditory processing disorder (CAPD), and hearing loss. When left untreated, these difficulties impair a person's capacity for efficient communication and may also have an adverse influence on their neurological functioning [19]. Middle ear infections and consequences from otitis are more common in children with ASD, which emphasizes the significance of regular middle ear exams and careful consideration of hearing impairment in this population [20]. Children with OME may experience learning difficulties and speech delays. If the condition is chronic, major side effects such as ear ossicular issues, hearing loss, tympanic membrane adhesion or rupture and even behavioral issues are likely [21].

Our research aimed at exploring the relation between iron deficiency anemia and recurrent otitis media in autistic children. Children in the study are between 6 and 10 years old which is the common age group for autism. Research has highlighted how

impactful the autism spectrum disorder is on every part of a child's life, as autism is a disorder that is prevalent in youngsters aged 3 to 8 years. The results of our study showed male children were more than female children, constituting 70% of the studied children. This agrees with Bener A. et al. [21] who stated that boys are four times more prone than girls to have autistic disorder, as autism risk factors have been linked to environmental, dietary, and genetic variables. The same age group findings in the current study agree with previous research, that found higher incidence of chronic suppurative otitis media among children aged 5 to 12 years. This could be attributed to the fact that this age group are more prone to upper respiratory infections, due to inadequate nutrition and intake. Insufficient dietary intake has been linked to a lower immune system, mucosal injury, and stunted growth in children, according to the research on the risk of CSOM in this age group [22]. Similarly, our results found a higher incidence of Otitis media in males, which had also been found in research by Jain et al. that indicated high incidence of CSOM in boys as much as 60%, CSOM is more common in males and is often detected at school age. This is because both male and female craniofacial anatomy differs in that male's eustachian tube is bigger and lies more horizontal than females, and their mastoid cavity is longer, their intracochlear distance is greater, and their eustachian tube is thicker. [23, 24].

The current study found hemoglobin levels to be significantly lower in children with OM ($p < 0.001$). Moderate anemia was observed in 54.3% of children. This agrees with the study of Bener A. et al. which confirmed that the deficiency of iron and anemia are common in autism. Autism has been linked to iron deficiency, and multiple studies have found iron deficiency anemia to be higher among children with autism than in the general population [21]. The current study found that children with autism had a higher risk of developing anemia, which was explained by the restrictive and picky eating habits that are common behavioral symptoms in children with autism [18]. Their restrictive dietary intake has been associated with finding lower levels of higher mean values of hemoglobin, ferritin, potassium, magnesium, calcium, phosphorous, glucose, hematocrit, WBC, and MCV, further affecting their proper development. [19].

Our results have found a higher incidence of otitis media with lower levels of serum iron and hemoglobin, which are consistent with the research done by Elemraid et al., who observed that 46.5% of patients with CSOM had decreased level of iron and the length of infection was longer. Earlier research stated that there was a strong association between the deficiency of iron and chronic ear infection stated that there was an elevation in the serum iron levels after giving the children with OM iron supplementation and there was a reduction in the incidence of ROM ($p < 0.001$) [25]. Iron is an important micronutrient for immune regulation, it serves in the proliferation and activation of immune cells such as macrophages, neutrophils, T cells, and B-cells. Iron deficiency causes dysregulation of the immune system, mainly via decreased response of T-cells to infectious agents and decreased bactericidal activity of macrophages [7]. The current results also agree with the findings of Purwanto et al. who found many children with iron deficiency to have chronic ear infections as much as 95.6%. In the literature, there is a relationship between the deficiency of iron and an increased risk of infection in children. This association is due to immune deficiency, mainly a decrease in the function of neutrophils, lymphocytes and macrophages. Iron deficiency anemia causes disruption in maturation and difference of immune cells, as well as disruption in moderating the innate and adaptive immune reaction [23, 26]. According to a study by Akcanet al., children with iron deficiency have a 3.3-fold higher chance of developing OM than those without the condition. We also agreed with Guneset al. that children with ASD had decreased levels of hemoglobin, hematocrit, iron, and MCV ($p < 0.05$). Additionally, IDA was found to be higher among intellectually disabled ASD individuals. The result might have something to do with the higher likelihood of feeding issues among people with intellectual disabilities. Food rejection, feeding skill deficiencies, food selectivity, and related behavioral issues are more prevalent in these children than in typical children [27].

Conclusion and recommendations

The risk of anemia in these patients may be associated with the following factors: the described limitations on feeding behavior, swallowing difficulties or the adequacy of food intake, potential macro and micronutrient deficiencies, and certain forms of chronic medication. These values should be examined as part of normal investigations because of the overlapping factors surrounding anemia [25].

To ascertain whether anemia is more common in such children and to evaluate the effectiveness of their low iron consumption, more research with bigger sample sizes and control groups would be beneficial.

Iron parameters should be assessed in children with iron deficiency anemia since it may be a risk for the occurrence of otitis media with effusion. so that comprehensive OM treatment and prevention can be implemented.

Regular otologic examination should be routinely done in children with autism, as they are a high-risk population for development of middle ear infections. Future research in studying serum iron and hemoglobin levels, its potential effect of the intellectual and communicative abilities in children with autismcould be of interest.

Conflicts of interest

The authors declare there are no conflicts of interest.

Authors' contributions

HTS did all the audiological assessment and testing, statistical analysis, writing manuscript.
GTO: did all the phonological assessment and statistical analysis.
All authors have participated sufficiently in the intellectual content, conception and design of this work or the analysis and interpretation of the data, as well as the writing of the manuscript.

Ethical considerations

The protocol was reviewed and approved by the ethical research committee of the National Nutrition Institute with approval number IN000167. The guardians of participants provided written informed consent. Research Ethics Committee – Federal Wide Assurance (FWA). FWA00014747. RHDIRB 2017103002

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