Screening the Egyptian Children with Metabolic Disorders Using the Modified Checklist of Autism

Original Article

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ABSTRACT

Background: The exact cause of autism spectrum disorder (ASD) cannot be defined but, it is proved by recent studies that there is great association between the diagnosis of ASD symptoms and presence of different metabolic disorders which should be taken in consideration in management of autistic children.

Aim of the Work: is to diagnose the presence of ASD among metabolic disorders affected children by screening using M-CHAT-R/F.

Patients and Methods: This is an analytical (observational) cross sectional research design. The study was done on a convenient sample of 100 children with a diagnosis of different Metabolic Disorders ranging age between (16-30) months, using the validated Arabic version of Modified Checklist of Autism- Revised and Follow up (M-CHAT R/F).

Results: there was unequal distribution of 13 types of metabolic disorders among the 100 children. Testing for ASD by use of M-CHAT-R/F found low risk (safe) in 22% of children, moderate risk in 58% of children and high risk for ASD in 20% of children.

Conclusion: Children with metabolic disorders are very susceptible to suffer from ASD. Physicians should work hard to recognize the early symptoms of autism to ensure early management and better prognosis.

Key Words: Autism, metabolic disorders, M-CHAT R/F.

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INTRODUCTION

Patients with Autism spectrum disorders (ASD) suffer from language problems, social difficulties, and monotonous repeated behaviors with varying severity in each patient[1].

There is a worldwide increase in the number of autistic children estimated by the WHO as 1 case diagnosed in every 100 children[2]. There is no definite cause of ASD, but research has accused the presence of physiological and metabolic system abnormalities that can't be explained by organ-specific dysfunction[3].

Metabolic disorders (MD) are implicated in several behavioral and neurological disorders of affected children[4]. Many MDs have been associated with ASD, and on top of these disorders are phenylketonuria and Homocystinuria[5].

The prevalence of mitochondrial disease in the ASD population is estimated to be about 5.0%, 500 times higher than that found in the general population[6].

Mitochondria are a vital source of energy in the central nervous system. They are also involved in the proliferation, differentiation, and maturation of neural stem cells, the formation of dendritic processes, developmental and synaptic plasticity, and cell survival and death. Thus, it is not surprising that multiple lines of evidence support the role of mitochondrial dysfunction in the etiology of ASD[7].

Although there is limited clinical evidence, research showed that therapy using the ketogenic diet improved

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ASD symptoms in 50% of autism patients who received this metabolic therapy[7].

Physicians can suspect autism around the age of 18–24 months; the characteristic symptoms of ASD can be differentiated from normal development and other developmental delay conditions[6]. But still, most cases are discovered around the age of 3 years. So, according to the recommendations of the American Academy of Pediatrics (AAP), early screening should be done for ASD at 18, and 24 months, especially in the high-risk groups[8].

Several screening tools have been developed to screen ASD. Among these tools is the Modified Checklist of Autism Revised and Follow-up (M-CHAT-R/F)[9]. It is used to screen ASD among children between 18 – 24 months and supplemented with a follow-up sheet to be more sensitive. Moreover, it is translated into Arabic and validated for Egyptian children[10].

Existing research has not adequately addressed the prevalence of ASD among children with metabolic disorders, especially in Egypt. To address this gap, this study will undertake a screening initiative for ASD within the Egyptian pediatric population with metabolic disorders, employing the Arabic adaptation of the M-CHAT-R/F for this purpose.

AIM OF THE WORK

To screen ASD among Egyptian children with metabolic disorders using the Modified Checklist of Autism-Revised (M-CHAT-R/F).

PATIENTS AND METHODS

Type of Study: It is an analytical (observational) cross-section study.

Patients: The study was applied to 100 children suffering from metabolic disorders. Children were conveniently selected from the outpatient clinic of Pediatric neurology in El-Demerdash Hospital

Inclusion criteria:

- Children with specific metabolic disorders.
- The child's age ranges between 18 - 24 months.

Exclusion criteria

- Children with hearing impairment.
- Children with visual impairment.

Procedures and clinical tools

Children were evaluated by an examiner who holds a master's degree in Phoniatrics using the assessment steps adapted from the language assessment protocol used at the Unit of Phoniatrics Ain Shams University, including the following:

1. Patient's history taking including child name, age, and sex.
2. General examination to exclude diagnoses interfering with assessment (visual or hearing impairments).
3. Validated Arabic version of Modified Checklist of Autism- Revised and Follow up (M-CHAT R/F)[9].

Validated Arabic version of Modified Checklist of Autism- Revised and Follow up (M-CHAT R/F)[10].

It is a parent’s interview screening tool to assess risk for ASD. It is formed of 2 sheets, Revised and Follow-up.

The M-CHAT-Revised was designed to detect most of the cases of ASD. However it was criticized as having a high false positive rate, so it was supplemented with the follow-up scoring sheet to be M-CHAT-R/F which has a higher sensitivity and fewer false positive results[9].

The scoring sheet of M-CHAT-R/F is composed of 20 questions, the response “No” indicates ASD risk in all items except (2, 5 & 12). The response “Yes” indicates ASD risk in items (2, 5 &12).

- Low risk scores (0-2) → if the child is less than 24 months, screen again after reaching 24 months. No further actions are required.
- Medium risk score (3-7) → get additional information about at-risk responses. The child should be rescreened at future well-child visits.
- High-risk score (8-20) → it is advisable to refer immediately for detailed evaluation and proper intervention.

Ethical considerations: An informed consent was taken from all the subjects' parents.

The study was approved by the Ethics Board of Ain Shams University. All participants in this study have given their written consent and the study protocol has been approved by the Ain Shams Institute's Ethical Committee of Human Research.

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RESULTS

This study was carried out on (100) Egyptian children diagnosed with a metabolic disorder in the pediatric neurology clinic.

The studied cases were distributed as 72% male and 28%females as shown in (Fig 1).

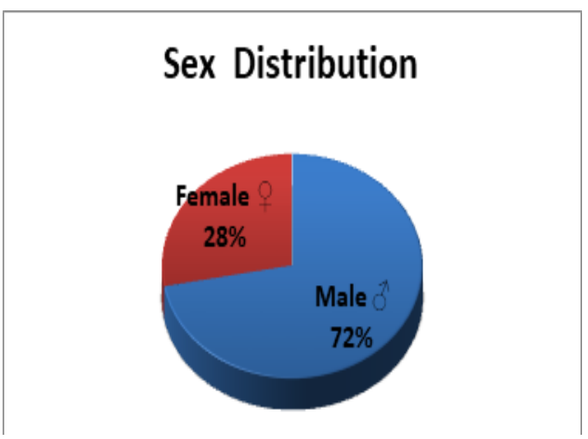

Fig. 1: Sex distribution in the study group (*n*=100).

The studied sample of 100 cases was unequally distributed among 13 metabolic disorders, where the most frequent disorders are 17 cases of mitochondrial disorder, 11 cases of phenylketonuria (PKU), and 10 cases of gluten defect. The least frequent disorders are neural ceroid lipofuscinosis (3%) and neurometabolic disorder (3%) as shown in (Table 1).

Table 1: Metabolic disorders distribution in the study group (*n*=100).

Metabolic Disorders	*N*	%
Mitochondrial disease	17	17.0%
PKU	11	11.0%
Gluten defect	10	10.0%
Tuberous Sclerosis	9	9.0%
G6PD	9	9.0%
Homocystinuria	8	8.0%
Wilson disease	8	8.0%
Glucose Transporter defect	6	6.0%
Glycogen storage disease	6	6.0%
Biotidinase deficiency	5	5.0%
Thiamine deficiency	5	5.0%
Neural ceroid lipofusenosis	3	3.0%
NeuroMetabolic disorder	3	3.0%

The distribution of studied cases according to the results of the screening test M-CHAT R/F was divided into 3 groups which are 22% of the studied cases have low risk, 58% have medium risk and 20% have high risk as shown in (Table 2).

Table 2: Results of M-CHAT R/F.

		N	%
M-CHAT R/F	Low risk	22	22.0%
	Medium risk	58	58.0%
	High risk	20	20.0%

The distribution of the cases of low, medium, and high risk for ASD according to the results of M-CHAT R/F in each group of the metabolic disorders shows that the groups of Gluten defect, Glycogen Storage Disease, and G6PD Deficiency have the highest percentage of the low-risk cases. (60%) of Gluten defect cases in our study had low risk, (50%) of Glycogen Storage Disease cases had low risk and (44.4%) of G6PD Deficiency cases had low risk. The groups of the neurometabolic disorder, Biotidinase Deficiency, and mitochondrial disorder had the highest percentage of medium-risk cases (100%), (80%) & (76.5%) for each group respectively. The groups of Homocystinuria, Tuberous Sclerosis, and thiamine deficiency had the highest percentage of the high-risk groups (50%), (44.4%) & (40%) for each group respectively as shown in (Table 3).

Table 3: Distribution of low, medium and high risk group among the metabolic disorders.

	M-CHAT R/F		
	Low risk	Medium risk	High risk
	N (%)	N (%)	N (%)
Mitochondrial disease	1 (5.9%)	13 (76.5%)	3 (17.6%)
Phenylketonuria	3 (27.3%)	6 (54.5%)	2 (18.2%)
Gluten defect	6 (60%)	3 (30%)	1 (10%)
Tuberous Sclerosis	0 (0%)	5 (55.6%)	4 (44.4%)
Glucose 6 phosphate Dehydrogenase Deficiency	4 (44.4%)	5 (55.6%)	0 (0%)
Homocystinuria	1 (12.5%)	3 (37.5%)	4 (50%)
Wilson disease	0 (0%)	6 (75%)	2 (25%)
Glucose Transporter defect	2 (33.3%)	3 (50%)	1 (16.7%)
Glycogen storage disease	3 (50%)	3 (50%)	0 (0%)
Biotidinase deficiency	0 (0%)	4 (80%)	1 (20%)
Thiamine deficiency	1 (20%)	2 (40%)	2 (40%)
Neoral ceroid lipofusuenosis	1 (33.3%)	2 (66.7%)	0 (0%)
NeuroMetabolic disorder	0 (0%)	3 (100%)	0 (0%)

DISCUSSION

ASD, being a puzzle-like disorder affecting long-life quality with an increasing prevalence as one of the most common child neuropsychiatric disorders; is a worldwide health concern. Our study aimed to detect the children at risk for ASD from a high-risk group e.g. metabolic Disorders by use of M-CHAT R/F as a screening tool.

In our study, 100 toddlers of the age range (18 - 24 months old) with different metabolic disorders were screened for ASD by application of the screening test validated Arabic version of M-CHAT R/F. This age group is recommended by Robins as symptoms of ASD appear in the early 2nd year of life[10]. The mean age was 21 (in months) with a standard deviation (SD) of 3.6%. Sex distribution in the study was (72%) males and (28%) females with male to female ratio (M/F ratio) of 2.57:1.

The current study detected according to the M-CHAT R/F results that the low-risk group (*n*=22) is 22% of the studied cases, the moderate-risk group (*n*=58) is 58%, and the high-risk group (*n*=20) is 20%.

According to the age, the mean age in the low-risk group was 19 with SD 5. The mean age in the medium-risk group was 18 with SD 7. The mean age in the high-risk group was 22 with SD 4. Screening at that early age is a proper time for early intervention and better outcomes. It is going with the recommendation of the American Academy of Pediatrics (AAP) to start the intervention as soon as possible once ASD is diagnosed. AAP also stated that interventions started before the age of 3 years have a greater positive impact than those started after the age of 5 years[11].

According to sex distribution in (low, medium and high-risk groups, the low-risk group had (62%) males and (38%) females with (M/F ratio) 1.6: 1. The medium-risk group had (69%) males and (31%) females with (M/F ratio) 2.2: 1. The high-risk group had (75%) males and (25%) females with (M/F ratio) 3:1, suggesting that males are more susceptible than females. It is near the ratio obtained by Loomes, & Mandy at 2017, ASD M/F ratio is about 3.3 to 1 detected by screening studies[12].

There is a great debate about the sex influence on ASD, some research states males are more likely than females to be diagnosed with autism and females are underdiagnosed due to gender bias in parental reporting, while others adopt theories e.g. different phenotypes and extreme male brain theory as an answer for sex ratio difference in ASD[12].

Our study sample included 13 MDs with different numbers of children in each disorder since the number is very small in some disorders which will not be sufficient to make a conclusion. We will discuss only 7 disorders which include enough cases.

Regarding the distribution of low, medium-risk, and high-risk groups among the 7 metabolic disorders:

Mitochondrial disease cases were the highest number in our study, with (76.5%) of patients in the medium-risk group, hence abnormalities in Ca2+ handling and ATP production in the brain mitochondria affect the synaptic transmission, plasticity, and synaptic development, contributing to ASD[13].

The second common MD in our study is Phenylketonuria (11 cases), which showed a high percentage of medium risk. This can be explained by the results of ***Jaco et al.*** which concluded that Phenylketonuria is the most common genetic metabolic disease with a well-documented association with autism spectrum disorders. It is characterized by the deficiency of the phenylalanine hydroxylase activity, causing plasmatic hyperphenylalaninemia and variable neurological and cognitive impairments[14].

Gluten defect cases revealed the highest percentage of low-risk (60%). However, there were trials to use a gluten-free diet to manage ASD. Recent research indicates there could be some links—possibly between ASD and celiac disease (which causes digestive and other symptoms) not with gluten defect[15].

All cases of Tuberous sclerosis complex (TSC) in our study showed medium or high risk for ASD. TSC is a multisystem autosomal dominant genetic disease that causes non-cancerous tumors to grow in the brain and on other vital organs[16]. Identified factors to cause ASD include the load of brain lesions, the size, and the location of the tuber (tumor)[17].

For G6PD Deficiency (44.5%) of cases were at low risk, 55.5% medium risk, and no high-risk cases. Although G6PD has been linked to developmental delay and ASD[18], the low incidence of ASD in our study can be explained by early discovery of cases with proper management.

Evidence suggests that impaired homocysteine metabolism in homocystinuria is linked to induced oxidative stress, mitochondrial impairment, and methylation impairment, all of which are involved in ASD pathology[19]. This explains that most cases of homocystinuria in our study showed medium and high risk for ASD.

Each child diagnosed with Wilson disease in our study has a medium or high risk for ASD. Wilson disease is characterized by copper depositions in the body, and deposits in the brain cause neurologic pathologies including autism[20].

CONCLUSION

There is an evident comorbidity between MD and ASD, although the exact pathophysiology is variable. Since most of MD are treatable. Phoniatricians dealing with ASD children should be aware of the enormous symptoms and variability of the MD, which may be causing or exaggerating the symptoms of ASD. ASD is a long-life-affecting disorder for the child and his/her family. So, early detection provides better intervention and a favorable prognosis.

RECOMMENDATION

1. Future research is recommended to correlate the controlled treatment of the metabolic disorder and the improvement of ASD symptoms or may lessen its incidence.

2. The screening test for ASD is widely used in pediatric clinics that treat high-risk groups, e.g., the pediatric neurology clinic.

3. Still precise follow-up for the risk group is mandatory to settle the diagnosis because sometimes the full-blown picture of ASD appears by the age of 4 years old.

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This paper has not been published in its current form or substantially similar form elsewhere including on a web and it has not been accepted for publication elsewhere

CONFLICT OF INTEREST

There is no conflict of interest.

AUTHORS CONTRIBUTION

Dina Ahmed Elrefaie formulated the idea and aim and conducted the research process.

Hassan H. Ghandour performed the writing and editing.

Lamiaa M. Abdel-wareth designed the work.

Mennatallah O. Shata provided the study material and interpretation of data.

Azza S. Abdel-Hakim acquired the data, applied the statistical techniques, and wrote the original draft.

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الكشف عن وجود اضطراب طيف التوحد لدى الأطفال الذين يعانون من اضطرابات التمثيل الغذائي

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الخلفية: لا يمكن تحديد السبب الدقيق لاضطراب طيف التوحد، ولكن أثبتت الدراسات الحديثة أن هناك ارتباطا كبيرا بين تشخيص أعراض التوحد ووجود اضطرابات التمثيل الغذائي المختلفة التي يجب أخذها في الاعتبار عند علاج الأطفال المصابين بالتوحد.

الهدف من العمل: هو تشخيص وجود التوحد بين الأطفال المصابين باضطرابات التمثيل الغذائي عن طريق الفحص باستخدام قائمة استبيان التوحد المعدلة.

الأساليب: هذا تصميم بحث تحليلي. أجريت الدراسة على عينة مختارة من ١٠٠ طفل تم تشخيص إصابتهم باضطرابات أيضية مختلفة تتراوح أعمارهم بين (١٨ - ٢٤) شهرا، باستخدام النسخة العربية المعتمدة من قائمة استبيان التوحد المعدلة.

النتائج: كان هناك توزيع غير متساو ل ١٣ نوعا من الاضطرابات الأيضية بين ١٠٠ طفل. اختبار وجود التوحد باستخدام قائمة استبيان التوحد المعدلة، وجدنا مخاطر منخفضة في ٢٢٪ من الأطفال، ومخاطر متوسطة في ٥٨٪ من الأطفال ومخاطر عالية لاضطراب طيف التوحد في ٢٠٪ من الأطفال.

الاستنتاج: الأطفال الذين يعانون من اضطرابات التمثيل الغذائي معرضون جدا للمعاناة من التوحد. يجب أن يعمل الأطباء للتعرف على الأعراض المبكرة للتوحد لضمان التدخل المبكر والتشخيص الأفضل.