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Prevalence and Risk Factors of Autism Spectrum Disorder in Children with Epilepsy

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Abstract

Background: The need for early detection and supportive therapy of Autism Spectrum Disorder (ASD) underlined the influence of screening for ASD in children with epilepsy as well as screening for epilepsy in ASD. This study aimed to explore the prevalence of autism in epileptic children in the northwest of Iran.

Methods: A case-control study was performed on 80 children aged 16 to 30 months, consisting of 40 with epilepsy as the case group and 40 with febrile seizure as a control group. The case group included children diagnosed with epilepsy, and the control group comprised children with recurrent febrile seizures who were matched by age and sex. Two questionnaires, Ages and Stages Questionnaire (ASQ) and Modified Checklist for Autism in Toddlers (m-CHAT), were utilized for developmental assessment and ASD screening, respectively. An experienced child and adolescent psychiatrist clinically diagnosed autism through relevant DSM-5 criteria.

Results: The studied children comprised 22 (55%) males and 18 (45%) females. Based on the M-CHAT screening questionnaire, 19 (47.5%) patients in the case group were positive for ASD. M-CHAT-positive patients were referred to the comprehensive autism center, and of whom, 4 (10%) patients met DSM-5 diagnostic criteria for ASD (definite ASD). In epileptic children with developmental delay, the overall prevalence of definite ASD was 18.2%.

Conclusion: The present study showed a high prevalence of autism among epileptic children, especially in developmentally delayed children; this demonstrated the need for autism screening in epileptic patients.

Key Words: Autism, Children, Epilepsy.

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1- INTRODUCTION

The definition of Autism Spectrum Disorder (ASD) is impaired social communication and specific behavioral patterns beginning early in life, with a prevalence under 1% worldwide (1, 2). The concomitant of autism and epilepsy has been debated for decades (3); this happens especially in association with intellectual disability that is possibly due to underlying components, including genetic, structural, and metabolic, that influence both diseases (3-5). ASD has been revealed to have a substantial genetic basis (6, 7). Numerous studies have shown the increasing rate of epilepsy among patients with autism and vice versa (4).

Research indicates a higher frequency of ASD among patients with epilepsy in comparison with the general population, despite limited studies on this relationship (8). It has been shown that epilepsy may enhance the risk of ASD from 5% to 37%. (8). A recent study in Brazil showed that ASD prevalence is substantially higher (23%) when compared with the general population (9).

The urgency and importance of early detection and supportive therapy of ASD are underscored by the findings of this study, highlighting the requirement of screening for ASD in epilepsy and epilepsy in ASD patients. (10).

Previous studies have reported various prevalence rates of autism among patients with epilepsy (8). However, data from Iran are scarce. This study aims to determine the prevalence of autism in epileptic children in the northwest of Iran, improving the way for further research and improvements in diagnosis and treatment of this disease.

2- MATERIALS AND METHODS

2-1. Design and population

A case-control study was performed on 80 children referred to Tabriz Zahra Mardani Azari Hospital (Tabriz, Iran) from February 2020 to February 2022 (40 epilepsy and 40 febrile seizure).

2-1-1. Inclusion and exclusion criteria

The inclusion criteria for the case group encompassed patients aged between 16 and 30 months with epilepsy and experienced seizures more than once a month. Epilepsy was defined by the International League against Epilepsy (ILAE) guidelines (11). Patients with chronic diseases, progressive neurologic illnesses, congenital metabolic disorders, and systemic diseases were excluded from the study. Patients with previous ASD diagnosis or autism-epilepsy syndrome, such as Dravet’s syndrome, were also excluded.

2-2. Procedure

Developmental and ASD screenings were performed using the Ages and Stages Questionnaire (ASQ) and Modified Checklist for Autism in Toddlers (M-CHAT). If the questionnaires scored two or more, the patients were referred to the Comprehensive Autism Center of Tabriz University of Medical Sciences, a leading institution in autism research, for additional follow-up on the definitive diagnosis of ASD according to the DSM-5 criteria (12). The patients with scores between 3 and 7 were considered moderate risk. Children with scores between 8 and 20 were deemed to be at high risk for autism.

2-3. Data Analysis

SPSS software was used to analyze the data. Descriptive statistics, including frequency, percentage, and mean ± standard deviation, were employed for statistical analysis. To compare qualitative findings, we used Chi-square, Fisher's exact and correlation tests. In this study, P-values <0.05 were considered statistically significant.

3- RESULTS

The main characteristics of the 40 case children with epilepsy and the 40 controls with recurrent febrile seizures, which were matched by age and sex, are presented in Table 1. The group with epilepsy consisted of 22 boys (55%) and 18 girls (45%). These children had a mean age of 23.88 months (± 6.4 months), at the time of data collection (age range: 16-30 months). The control group, which included children with febrile seizures, also comprised 22 boys (55%) and 18 girls (45%), with a mean age of 23.85 ± 6.1 months at the time of screening (age range: 16-30 months).

Table-1: Characteristics of the 40 children with epilepsy (case) and 40 children with recurrent febrile seizure (control)

Demographic data:	Case group	Control group	P value
Mean age	23.88±6.4	23.85±6.1	0.830
Sex	Male: 22 (55%) Female: 18 (45%)	Male: 22 (55%) Female: 18 (45%)	
Seizure type	Focal: 9 (22.5%) Generalized: 31 (77.5%)	Focal: 4(10%) Generalized: 36 (90%)	0.225
ASQ	Normal: 18 (45%) Abnormal: 22 (55%)	Normal: 39 (97.5%) Abnormal: 1 (2.5%)	P<0.05
m-CHAT	Positive: 19 (47.5%) Negative: 21 (52.5%)	Positive: 0 (0 %) Negative: 40 (100%)	P<0.05
Definite ASD	Positive: 4 (10%)	Positive: 0 (100%)	P<0.05

ASQ: Ages and Stages Questionnaire

m-CHAT: Modified Checklist for Autism in Toddlers

In the case group the mean age at the seizure onset was 11.51 + 7.12 months (range: 1-30 months). Among 40 patients, ten children (25%) had epilepsy with structural causes. Nine (22.5%) and 31 (77.5%) children were diagnosed with focal and generalized seizure types, respectively.

The autism screening with the M-CHAT questionnaire revealed that in case group 19 (47.5%) patients had at least two positive symptoms in the screening test, and the remaining 21 (52.5%) had no symptoms of ASD. Among patients with positive screening, 15 (37.5%) were regarded as a high-risk group, and 4 (10%) were scored as a low-risk group. M-CHAT-positive patients were referred to the comprehensive autism center, among whom 4 (10%) patients met DSM-5 diagnostic criteria for ASD (definite ASD). Three of them (7.5%) were high-risk boys, and one patient (2.5%) was a low-risk girl. There was no positive screening test (P<0.05) among the control groups.

The developmental screening by the ASQ questionnaire revealed that 22 patients (55%) had developmental delays in the case group, and the remaining 18 (45%) had normal development. Of 22 patients with abnormal ASQ scores, 14 (35%) had abnormal scores in all five domains of the ASQ questionnaire. The most positive results of the screening test were found in communication, problem-solving, and the personal-social domain (Table 2). In the control group, one patient (2.5%) had an abnormal developmental delay in gross motor and speech domains.

Of 22 cases with abnormal ASQ, 16 (72.7%) had abnormal M-CHAT, but only

3 (16.6%) of patients with normal development had abnormal M-CHAT (P<0.01). All the children with definite ASD also had abnormal ASQ (P>0.05). In epileptic children with developmental delay, the overall prevalence of definite ASD was 18.2%.

Table-2: Association between ASD screening results and the five domains of ASQ in children with epilepsy

ASQ domains	m-CHAT results		p-value
	Positive (16)	Negative (6)	
communication	16 (100%)	3 (50%)	0.013
Gross motor	11 (68.8%)	6 (100%)	0.266
Fine motor	13 (81.2%)	4 (66.7%)	0.585
Problem solving	15 (93.8%)	3 (50%)	0.046
Personal social	16 (100%)	2 (33.3%)	0.002

Among 40 patients with epilepsy, nine patients (22.5%) had a focal seizure, and 31 patients (77.5%) had a generalized seizure. No generalized seizure patients and about half of focal seizure patients (44.4%) met the DSM5 criteria for ASD (P<0.01). 56% of patients with uncontrolled epilepsy were at high ASD risk on M-CHAT, while none of the patients with controlled epilepsy were at high ASD risk (P<0.01).

4- DISCUSSION

This study represented the first work of ASD in young children diagnosed with epilepsy in the northwest of Iran. ASD and epilepsy are distinct yet overlapping disorders (13). The bond between epilepsy and ASD has been the focus of many studies (13, 14). While most of the existing literature has shown an increased risk of epilepsy among patients with ASD, fewer studies have addressed the prevalence of ASD among patients with epilepsy. A recent systematic review has suggested that regarding ASD symptoms, younger children with epilepsy need more considerations (15).

The results of this study indicated that the prevalence of ASD among epileptic patients was 10%. This prevalence was significantly higher than that of other non-epileptic recurrent seizures, such as recurrent febrile seizures.

The prevalence of ASD is approximated to be 70-60 per 10,000 individuals. The prevalence of epilepsy in patients with autism ranged between 1.8 and 60% with a median of 12.1%. Conversely, the prevalence of autism in people with epilepsy ranged between 0.60 to 41.9% with a median of 9.0% (3). Berg et al., showed that 5% of children with epilepsy had autism disorders (16). Similarly, Jokiranta et al. showed a prevalence of epilepsy of 6.6% in children and adolescents (17). Fisher et al. reported an autism prevalence of less than 7% in children with epilepsy (18). Several mechanisms may explain the link between ASD and epilepsy. Certain epilepsy syndromes and specific genetic factors are associated with a higher risk of ASD (19, 20).

This study made known that children with epilepsy who had developmental delays were at high risk of developing ASD and should undergo diagnostic and screening tests for ASD, as 72.7% of epileptic children with abnormal ASQ had positive symptoms of ASD in the m-CHAT screening tests, and all the children with confirmed ASD had abnormal ASQ.

Children who face both epilepsy and intellectual disabilities are at a significantly higher risk of developing ASD. In contrast, children with epilepsy who do not have intellectual disabilities show a lower risk of developing ASD (15).

It is important to note that intellectual disability is a significant risk factor for epilepsy in patients with ASD (21). Fisher et al., found that none of the autism-positive children had normal developmental screeners (18). Furthermore, children who have both epilepsy and Intellectual Disability (ID) are at greater risks of developing ASD compared to those with epilepsy and average intellect (22). Further, among children with epilepsy, those with intellectual disability face the highest risk of developing ASD. Therefore, the risk of ASD is low in children with epilepsy who do not have intellectual disability (15).

This study finding has suggested the importance of ASD screening in epileptic patients with abnormal development, especially in the communication and personal-social domains.

Research has shown that the male-to-female ratios in prevalence surveys can range from 1.33:1 to 15.7:1 (commonly a consensus ratio of 4:1) (23). A meta-analysis revealed that the rate of epilepsy is lower in males with 18.5% compared to 34.5% in females (21). Additionally, Berg et al. indicated that male patients with epilepsy are twice diagnosed with autism than their female counterparts (16). Viscidi et al. also showed that autism is more common in boys (24). However, in this study, we did not observe any significant distinction between boys and girls. Moreover, females with autism frequently have more severe intellectual disabilities compared to males.

Currently, there is no specific seizure type or epilepsy syndrome in association with ASD reported in the literature (21). However, large studies have indicated that focal seizures occur more frequently than primary generalized seizures (25). In a population-based study, it was found that 73% of patients with ASD experienced focal seizures, while only 27% had primary generalized seizures (21). In the present study, about half of the patients (44.4%) with focal seizures met DSM-5 criteria for ASD.

Moreover, Jokiranta et al. (17) informed that the prevalence of autism is notably higher among individuals suffering from uncontrolled epilepsy. Parmeggiani et al. demonstrated that the frequency of autism was considerably lower in patients with controlled epilepsy in comparison with uncontrolled ones (26). In this study, two important prognostic factors for the development of ASD were developmental delay and uncontrolled epilepsy. However, due to the small sample size, further research with larger sample sizes is needed to establish a precise correlation.

4-1. Limitations of the study

The main limitation of this study was the small sample size of patients with epilepsy, which suggests the need for further studies with larger samples. However, this limitation does not diminish the importance of ASD screening in patients with epilepsy.

5- CONCLUSION

The current study makes known a significant prevalence of autism among children with epilepsy, especially with developmental delays. This underlines the consequence of early screening for autism in patients with epilepsy, which may provide valuable insights to health personnel and researchers.

6- ETHICAL CONSIDERATIONS

The Organizational Committee of Research Ethics approved the study

protocol, Tabriz University of Medical Sciences (IR. TBZMED.REC.1398.052).

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