Original article / *Araştırma*

Chromosomal aberrations in children with autism spectrum disorders in Upper Egypt

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ABSTRACT

Objective: *The pathogenesis of autism spectrum disorders (ASD) is complex and still not clear. Genetic factors contribute to the occurrence of ASD. However, the genetics of ASD is highly heterogeneous. Chromosomal aberrations have a key role to the genetic abnormalities of both syndromic and non-syndromic ASD.* ***Methods:*** *In our study, we conducted karyotyping analysis in a sample of 231 Egyptian children with ASD aged 3-13 years (132 males and 99 females) from five Governorates in Upper Egypt.* ***Results:*** *Eleven patients (4.7%) were found to have chromosomal abnormalities in this study. We found five patients having sex chromosome aneuploidy, including two patients with Turner syndrome, two with 47,XYY and one with 47,XXY. In addition, we detected three patients have Down syndrome, one patient has monosomy 1p36, one patient has Williams-Beuren syn-drome and one patient has a deletion of the long arm of chromosome 13.* ***Conclusions:*** *The present study rein-forces the findings of the association between some chromosomal aberrations and ASD. Further investigations into these regions may lead to discovery of new genes involved in ASD. The present study directs the attention of the clinicians about the importance of karyotyping in the evaluation of ASD patients.* ***(Anatolian Journal of Psychiatry 2017; 18(3):243-249)***

Keywords: *autism, chromosomal aberrations, karyotyping*

Yukarı Mısır'da otizm spektrum bozukluğu olan çocuklarda kromozomal sapmalar

ÖZ

Amaç: *Otizm spektrum bozukluklarının (OSB) patogenezi karmaşıktır ve tam olarak açık değildir. Genetik etkenler OSB'nin ortaya çıkmasına katkıda bulunur. Bununla birlikte, OSB'nin genetiği son derece heterojendir. Kromozomal sapmalar sendromik olan ve sendromik olmayan OSB'nin ikisinde de genetik anormalliklerde kilit rol oynarlar.* ***Yöntem:*** *Çalışmamızda Yukarı Mısır'daki beş ilden 3-13 yaşları arasındaki (132 erkek, 99 kız) 231 Mısırlı çocuk örnekleminde karyotipleme yaptık.* ***Sonuçlar:*** *Çalışmamızda 11 (%4.7) hastada kromozomal anormallikler bulundu. Beş hastanın cinsiyet koromozomu anoploidisinin olduğunu bulduk; iki hastada Turner sendromu, iki hastada 47,XYY, bir hastada 47,XXY vardı. Ayrıca üç hastada Down sendromu, bir hastada monozomi 1p36, bir hastada Williams-Beuren sendromu, bir hastada kromozom 13'ün uzun kolunda delesyon saptadık.* ***Tartışma:*** *Bu çalışma OSB ve bazı kromozomal sapmalar arasında ilişki bulgularını destekler. Bu çalışma, OSB hastalarının değerlendirilmesinde karyotiplemenin önemi konusunda klinisyenleri uyarıcıdır.* ***(Anadolu Psikiyatri Derg 2017; 18(3):243-249)***

Anahtar sözcükler: *Otizm, kromozomal sapmalar, karyotipleme*

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INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental syndrome. It begins before three years of age. ASD is characterized by pervasive deficits in social interaction, impairment in verbal and nonverbal communication, and stereotyped patterns of interests and activities.[1,2] The pathogenesis of ASD is bewildering. No known causes have been identified to explain the occurrence of ASD, which can be attributed to complex behavioral phenotypes as well as the involvement of various genetic and environmental factors in the etiology of autism.[1-3] Owing to the high prevalence of ASD, long-term impairment, high genetic component, and lack of effective prevention and treatment, ASD has been prioritized for genetic studies.[3]

The genetic construction of ASD is highly complex and heterogeneous. About 10% patients with ASD were comorbid with other syndromes or disorders with recognized genetic defects, e.g. Rett's syndrome, Fragile-X syndrome, phenylketonuria and Klinefelter syndrome.[3,4] However, the genetic causes of most ASD patients continue undefined. Multiple recent genetic methods, such as linkage and association studies, have been carried out to identify the susceptibility loci and the new genes in-volved in ASD without any consistent results.[5,6] This may be due to multiple factors including genetic heterogeneity of the ASD phenotype, the contribution of numerous interacting genes and variability in the expression of these genes. Moreover, various epigenetic mechanisms, such as parental imprinting and X-inactivation, may affect the susceptibility for ASD.[7] Conventional karyotyping studies reported that about 5-12% of patients with ASD were associated with chromosomal structural aberrations.[3,8] The aim of this study was to investigate karyotype abnormalities in a cohort of Egyptian children with ASD.

METHODS

The present study included 231 Egyptian children with ASD aged 3-13 years (132 males and 99 females) from 5 Governorates in Upper Egypt. All patients were recruited from the Neuropediatric Clinics Assiut, Qena and Aswan University Hospitals and five private centers for autism in Upper Egypt. An informed consent was obtained from each legal guardian of all patients before enrollment in the study. The study was approved by Qena Faculty of Medicine Ethical Committee, South Valley Univer-sity, Egypt.

All cases were evaluated according to the following:

1. Initial clinical and psychiatric assessment: The ASD diagnosis was confirmed using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).[9] Also, structured parent interviews of at least two hours proved the autistic manifestations. Later on, another three hours-sessions were used for the assessment of autism severity according to the Childhood Autism Rating Scale (CARS).[10] CARS evaluates behavior in 14 domains that are affected by ASD, plus one parameter of the general impression of autism. The 14 domains are: 1) relating to people; 2) imitation, social-emotional understanding; 3) emotional response, emotional expression and regulation of emotions; 4) body use; 5) object use, object use in play; 6) adaptation to change, adaptation to change/restricted interests; 7) visual response; 8) listening response; 9) taste, smell, and touch response and use; 10) fear or nervousness, fear or anxiety; 11) verbal communication; 12) nonverbal communication; 13) activity level, thinking/cognitive integration skills; and 14) level and consistency of intellectual response. The examiner assigned scores between 1 and 4 for each domain: one indicates normal behavior appropriate for age level (no signs of autism) while four indicates a severe deviance with respect to the normal behavior (severe symptoms of autism). The scores for the single items are added together into a total score. The maximum CARS score is 60, and the cutoff for autism is 30. A total score between 15 and 29.5 is considered non-autistic. Scores of 30.5 to 37 were rated as mildly-moderately autistic, while scores above 37.5 were rated as severely autistic.[10,11] It was carefully collected a detailed history from the parents about each child that were included in the study. The anamnesis included information about the family history of consanguinity, similar conditions of ASD in the family, social activities, self-care, and time of onset of the autistic manifestations. Also, the prime investigator carried out meticulous physical and neurological examinations (including sensory, motor, and autonomic evaluations) of all the patients.

2. Full Scale Intelligent Quotient (FSIQ) Test: By applying Stanford Binet Intelligence Scale, Fourth Edition; the test is valid by using factorial validity, criterion validity and also some studies

operate in the culture of Egypt that subtests of Stanford-Binet (fourth ed.).[12]

3. Karyotyping: A venous blood samples (1 ml) were obtained from all cases under com-plete aseptic conditions. Phytohemagglutinin stimulated peripheral blood lymphocytes were cultured according to the methods of Verma and Babu.[13] The culture incubated for 72 hours at 37°C, and then harvested using colchicine solution. Metaphase spreads were treated with trypsin to obtain the standard G (Giemsa)-banding pattern. For any numerical or structural abnormalities, metaphases were analyzed and karyotyped.

4. Fluorescence in situ hybridization (FISH): The diagnosis of William syndrome was confirmed by using the FISH test. This technique enables the determination of a specific deoxyribonucleic acid (DNA) sequence in a chromosome band. The technique involves the hybridization of a fluorescent-labelled probe to its complementary DNA segment within a metaphase chromosome. The probe is visualized with fluorescence in the FISH technique. In our study, the hemizygosity for the elastin gene was analyzed using the LSI Williams syndrome region DNA probe (VYSIS®), according to Pinkel et al.[14] This is a specific-locus probe marked with Spectrum Orange TM dye, which contains the locus of the ELN, the locus of the LIMK1 gene, and the locus of D7S613, a marker of chromosome 7. The control probe marked with Spectrum Green TM is included in the mixture and corresponds to loci D7S486 and D7S522 located in the 7q31 band. The presence of only 1 red signal (elastin gene) and 2 fluorescent green signals (markers of chromosome 7) indicates deletion of the elastin gene in one of the chromatids of chromosome 7, confirming the WBS diagnosis. In this case, the patient is considered FISH positive. The individual who has 2 red signals (presence of the elastin gene in both chromatids of chromosome 7, and 2 green signals is considered FISH negative.

RESULTS

The demographic and clinical data of the studied cases were described in Table 1, which showed the age, sex, CARS scores, FSIQ. Eleven patients (4.7%) were found to have chromosomal abnormalities in our study (Table 1). We found five patients having sex chromosome aneuploidy, including two patients with Turner syndrome, two with 47,XYY and one with 47,XXY (Klinefelter syndrome). In addition, we detected 3 patients have trisomy 21 (Down syndrome), one patient has monosomy 1p36, one patient has a deletion of the long arm of chromosome 7 (7q 11.23) Williams-Beuren syndrome and one patient has a deletion of the long arm of chromosome 13.

Table 1. Summary of all cases with autism and chromosomal abnormalities

Patient number	Gender	Chromosomal aberrations	Main clinical features	CARS scores	FSIQ
1	Male	Trisomy 21	Mongloid facies, Simian crease, atrial septal defect	31	66
2	Female	Trisomy 21	Mongloid facies, Simian crease,	34	58
3	Male	Trisomy 21	Mongloid facies, Simian crease, syndactyly, atrio-ventricular canal	31.5	50
4	Female	Turner 45X	Neck webbing, edema of feet, Short fingers	35.5	98
5	Female	Turner 45X	Neck webbing, cubitus valgus	33.5	88
6	Male	47,XXY	No abnormal features	37.5	95
7	Male	47,XYY	No abnormal features	35	102
8	Male	47,XYY	No abnormal features	31.5	105
9	Male	Del 13q	Hypertelorism, flat nasal bridge	32	99
10	Male	Del 7q	Elfin facies, full cheeks, long philtrum	33.5	87
11	Male	Del 1p36	Hypertrichosis, self-destructive behavior, high forehead and low-set ears	42	43

The details of the clinical and experimental findings of patients with chromosomal abnormalities are given below:

Trisomy 21 (Down syndrome): Three patients have the diagnosis of Down syndrome. Their ages were 3.5, 6 and 8.5 years. Two males,

their karyotypes were (47, XY+21); cases (1 and 3) and one female her karyotype was (47, XX+21); case number 2. All cases have Mongloid facies. Congenital heart diseases were found in two patients (atrial septal defect in case 1 and atrio-ventricular canal in case 3). Delayed milestones were present in all cases. FSIQ ranged from 50-66 and CARS scores ranged 31-34 (Table 1). There was no family history of neuropsychiatric disorders, any maternal infection or exposures to drugs during the pregnancy in the three cases.

Turner syndrome: Two females (cases 4, 5) have a diagnosis of Turner syndrome. Their karyotypes were 45X. The clinical features of case 4 included: neck webbing, feet edema and short fingers. She is 4 years old. She had a history of recurrent neonatal convulsions until the age of 3 months. Her CARS score was 35.5. FSIQ was 98. Case 5 has neck webbing, micrognathia, high arched palate and cubitus valgus. She is 5 years old. Her CARS score was 33.5 and FSIQ was 88. There was no family history of neuropsychiatric disorders in both patients.

47,XXY and 47,XYY: Three patients had sex chromosome aneuploidy, including two cases of 47, XYY (cases 6 and 7) and one patient had 47,XXY (Klinefelter syndrome); case 8. There were no dysmorphic features in the three patients (Table 1).

Deletion of the long arm of chromosome 13: One male patient (case 9), he is 6y old. He has a deletion of the long arm of chromosome 13. His karyotype (Figure 1) was 46,XY, del (13)(q22). He was born at 9 months' pregnancy of non-consanguineous parents. Clinically he has hypertelorism, flat nasal bridge. His CARS score was 32 and FSIQ was 99.

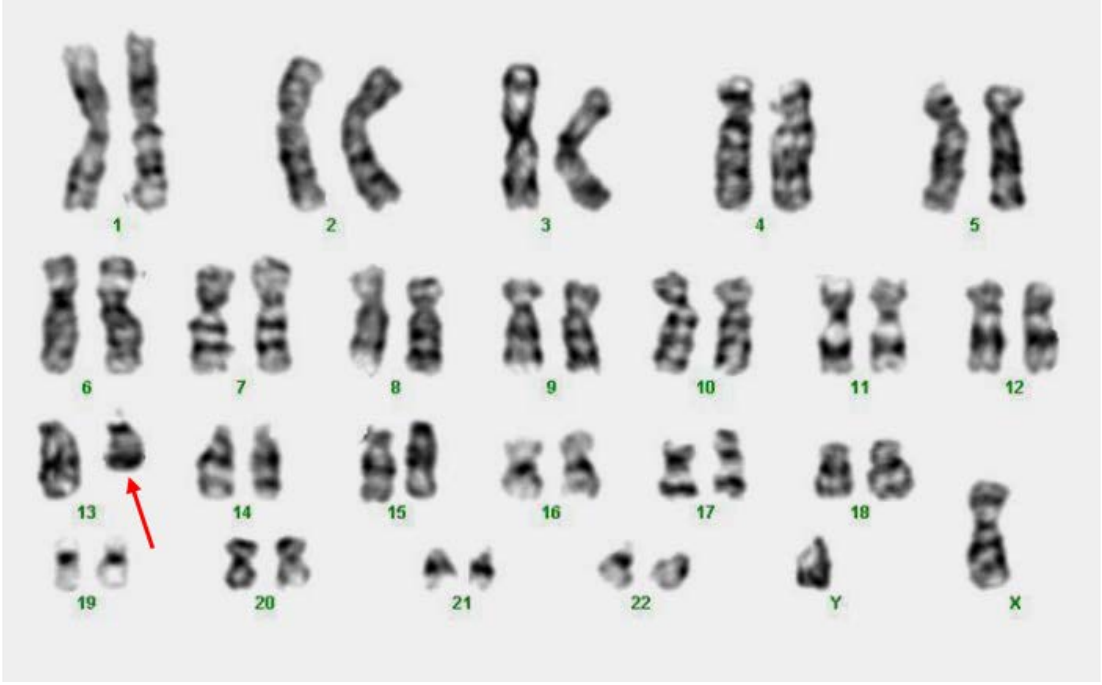

Figure 1. Karyotype of case number 9; the arrow shows the deletion of long arm of chromosome 13

Williams syndrome: One male patient (case 10), he is 9.5y old. He has a deletion of the long arm of chromosome 7. His karyotype (46XY, del (7q 11.23) was confirmed by FISH. He was born normally at 9 months' pregnancy of an uneventful pregnancy. Clinically he has elfin facies (flat midface with full and dependent cheeks, long philtrum and thick lips) and phonological errors. His CARS score was 33.5 and FSIQ was 87.

Monosomy 1p36: One male patient (case 11), he is 4.5y old. He has severe autism (CARS 42), mental retardation with FISQ 43, hypertrichosis, self-destructive behavior, high forehead and low-set ears.

DISCUSSION

Structural chromosomal aberrations including deletion, duplication, translocation, and inversion has been identified in some individuals with autism spectrum disorder, but their full etiologic role remains unidentified.[7,8] In this study, we conducted karyotyping in a sample of Egyptian children with ASD from five Governorates in Upper Egypt. 4.7% of our patients were found to have chromosomal abnormalities (Table 1). In agreement with our results the previously cytogenetically detectable chromosome aberrations were found in 5-12% of ASD cases with a range from 0% to 54%. The highest incidence of these abnormalities was found in syndromic forms of ASD.[3,7,8,15] Marshall et al.[8] studied 427 ASD patients by karyotyping; they reported chromosomal rear-rangements in 4.2% of ASD individuals, and 3.3% of the patients had cytogenetic abnormallities. Wassink et al.[16] studied 278 subjects with ASD; they found 9.0% had some sort of identifiable abnormality. Six subjects (2.2%) had a fragile X (q27.3), five (1.8%) had another form of sex chromosome abnormality, and 5% of the patients had autosomal abnormalities. Li et al.[17] reported that 11.5% out of 104 patients with ASD had chromosomal abnormalities, including eight patients with fragile X syndrome, two patients with Down syndrome, one patient with a reciprocal translocation between chromosomes 5 and 6, and one patient with Y inversion. In contrast to our study and the previous reports; Liao et al.[18] studied 500 patients with ASD, including 447 males and 53 females. Only 0.8% of ASD patients were found to have gross chromosomal abnormalities, including two patients with 47,XXY (Klinefelter syndrome), one patient with 47,XYY, and one patient with a reciprocal translocation between the long arms of chromosomes 4 and 14, designated t(4;14q31.3;q24.1).

The sex chromosomes were the most common aberrations in our study. Two patients have 47,XYY, two patients have Turner syndrome (45,X) and one patient has Klinefelter syndrome (47,XXY). The association between sex chromosomes and ASD has been previously demonstrated,[16,18] although the specific nature of the association remains unclear.[16]

Autism has been described in various cases of Turner syndrome patients.[19,20] In one study,[20] autism was observed in five out of 150 individuals with Turner syndrome (3%). Autistic features have been described in Turner syndrome subjects with reported 75- to 500-fold increased risk of autism compared with the general population. Females with Turner syndrome showed deficits in face recognition and in affect recognition on facial expressions.[19-22] The association is probably due to an imprinted X-linked locus affecting cognitive function and not expressed from the maternally derived X chromosome. It has been reported that 45,X females with the maternally inherited X chromosome have reduced social cognition compared with 45,X females with a paternally inherited X.[22]

Klinefelter syndrome has been well characterized in the medical literature. These patients have a high incidence of psychiatric disorders, behavioral problems, and cognitive impairments. Several case reports have been published describing the relationship between males with Klinefelter syndrome and ASD. The prevalence of psychiatric problems increased in patients with Klinefelter syndrome.[18,23,24] Patients with XYY syndrome are also susceptible to ASD, which has been reported by previous investigators.[18,24] Consequently, clarification of molecular mechanism of the link of sex chromosomes and ASD should shed some light on the pathogenesis of ASD. Taken our finding with the previous reports together, these sex chromosome abnormalities may harbor autism susceptibility genes and should continue to receive attention in spite of limited findings.

Previously, the dual diagnosis of ASD and Down syndrome has been considered to be somewhat rare. However, several studies that have used standardized ASD-specific assessments, have reported that the dual diagnosis of both disorders may be more common than previously supposed, with prevalence rates ranging from 5% to 39%.[25-27] Moss et al.[25] evaluated the proportion of patients with Down syndrome who met criteria for autism spectrum disorder (ASD) on the Social Communication Questionnaire. They reported that the proportions of patients with Down syndrome meeting the ASD and autism criteria were 19% and 8%, respectively. These findings are in agreement with the previous prevalence estimates reported by several studies.[26,27] Chromosome 7 includes over 150 million nucleotides and 1917 gene structures. A large collection of published and unpublished cases of autism with cytogenetic abnormalities of chromosome 7 is presented on the website of The Centre for Applied Genomics (www.chr7.org). Williams syndrome is a congenital developmental disorder caused by a hemizygous contiguous gene deletion on

chromosome 7q 11.23. Many studies included case reports of patients with Williams syndrome and ASD without any specific genetic information.[28-30] Leyfer et al.[29] found 9 children who met ASD criteria in a cohort of 128 children with Williams syndrome aged 4-16 years. Martens et al.[30] reported ASD in 48 patients (8%) from 599 patients with Williams syndrome.

Few case reports have been published describing the relationship between chromosome 1 and 13 aberrations and ASD.[31-34] We found two autistic children, one with a deletion of the long arm of chromosome 13 [46,XY, del (13) (q22)] and one with monosomy 1p36. The 13q- syndrome is caused by structural and functional monosomy of the 13q chromosomal regions. Patients with 13q partial deletions may have widely varying phenotypes, but the most common clinical features include moderate, severe mental and growth retardation, craniofacial dysmorphisms, hand and foot anomalies, and brain, heart and kidney defects.[34] 1p36 deletion syndrome was described for the first time in the late 1990s, although the first case of a child with a deletion of 1p36 was published in 1981. The disorder is now believed to affect one in 5,000 newborn babies, making 1p36 deletion sydrome one of the most commonly observed chromosome deletion disorders. There have been some reports of autistic behaviors in children with 1p36 deletion syndrome, although this is very rare.[31-35]

CONCLUSION

Gross chromosomal abnormalities, such as aneuploidy, deletions, and rearrangements, have been reported in the many studies. In our survey, abnormalities were found in chromosomes 1, 7, 13, 21, X and Y. The present study reinforces the findings of the association between some chromosomal aberrations and ASD. Further investigations into these regions may lead to discovery of new genes involved in ASD. The present study directs the attention of the clinicians about the importance of karyotyping in the evaluation of ASD patients.

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