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Case Series

Molecular genetics in autism spectrum disorder: a case series

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ABSTRACT

Autism spectrum disorder (ASD) has emerged as a fairly common yet heterogeneous condition. More evidence towards a large number of specific genetic variations in ASD are now identified. Often we encounter difficulties in counselling the parents on the disease origin. We present a case series of 6 children including a pair of twin sibling who were diagnosed as ASD with a definite genetic aetiology. These children belonged to the age group of 3 to 15 years and were diagnosed as ASD as per DSM V criteria. Of the 6 children, two were otherwise clinically normal and remaining four children had associated medical conditions including hypocalcemia, severe hypotonia, seizures, cardiomyopathy, intellectual disability and neuroregression. In view of an unrecognised aetiology and children being first born in the family, parents were counselled for a genetic evaluation. Genetic test reports revealed gene variation pathogenic for ASD, of which 4 of them had known syndromic association. Though intervention would mostly remain the same, genetic aetiology helped us in prognosticating and improved the family's outlook towards the disease. Hence it is desirable to identify genetic variations in all possible ASD cases as it has the potential to improve family planning, trigger screening for co-occurring medical problems, aid the prognosis, and start specific interventions.

Keywords: ASD, Genetics, Molecular gene study

INTRODUCTION

The study of autism started many decades ago and was first described in the year 1943 by the Austrian doctor Leo Kanner, in his scientific paper "Autism disturbances of affective contact".[1] The prevalence of autism has risen over the last few decades from around 2-4 in 10,000 to an estimate of 1%.[2] ASD is a heterogeneous disorder that can reveal a specific genetic disease and there are evidences in literature supporting ASD to its association with a wide variety of genetic conditions. We have now progressed from a time when role of genetics in ASD was unknown, to an era when the first twin and family studies showed autism to be one of the most highly heritable disorders.[3] Molecular genetic investigations are on the rise and have recently led to an increasing number of reported autism gene discoveries aiding to better understanding of autism. It is very evident from molecular genetic studies that autism is not only clinically heterogenous, rather highly heterogeneous in terms of genetic etiology at a molecular level. Increasingly, ASD have been described in individuals with a range of different genetic syndromes including: Tuberous sclerosis complex, fragile X, Cornelia de Lange, Down, Angelman, Coffin-Lowry, Cohen Laurence-Moon-Biedel, Marinesco-Sjogren, Moebius, Rett and Williams syndromes.[4,5] We report six children including a pair of twin sibling that illustrate the need for a genetic workup in ASD.

CASES SERIES

Case 1

A 3-year-old girl born of non-consanguineous marriage was brought for language regression and mild motor

delay. She was born out of normal delivery and normal development was observed till the age of two years following which there was regression in her language milestones. She also had seizures from the age of two years. Clinical examination carried out at the time of initial presentation revealed repetitive hand wringing movements, irritability, sleep disturbances, loss of speech, and autistic behavior. Paraclinical findings were non-contributing. The clinical findings prompted suspicion of Rett syndrome, and the molecular genetic test was carried out. It revealed a heterozygous nonsense variation in the exon three of the MECP2 gene that resulted in the stop codon as well as the premature truncation of the protein at codon 267, diagnostic of the Rett syndrome.

Case 2 and 3

A pair of fourteen-year-old twin siblings with no consanguinity were referred to our centre at age of six years for evaluation of delay in attaining milestones, poor attention and difficulty in communication. They had recurrent episodes of upper respiratory infections and swallowing difficulties. Both twins had acyanotic congenital heart disease-Atrial septal defect at two months of age and device closure was done by age of three years. Clinical examination of both revealed stereotypic movements involving jaw, lips and hand with dysmorphic facies, hyperextensibility of fingers, and mild kyphoscoliosis. In addition second twin had behavioural disturbance and significant mannerism in form of finger fidgeting. Ophthalmologic and auditory examination were normal. Blood investigation revealed hypocalcemia in first twin which was persistent even after treatment while calcium levels were normal in second twin. MRI scan of brain was normal for both. Video EEG done in second twin showed generalised epileptiform activity with eye closure discharge while it was normal for the first twin. Whole exome sequencing was done in view of multiple system involvement suspecting a genetic cause. Report showed the 22q11.21 gene deletion diagnostic of the Di George syndrome.

Interestingly, the family had denied the diagnosis of ASD initially and early interventions, until a genetic aetiology was identified.

Case 4

Another 2-year-old Autistic girl with 3rd degree consanguinity presented to our centre with convulsions, global developmental delay and severe hypotonia. According to the mother the problem had started since 8 months of age. She has noticed her child developmentally lacking behind other children of the same age and sex. There was no other member of the family suffering from the disease. On examination, she had severe hypotonia. Her vision, hearing and MRI brain were normal. EEG showed abnormal epileptiform activity. Whole exome sequencing was done and report showed a heterogeneous missense variation in exon 21 of the TSC gene that results in amino-acid substitution of leucine for glutamine at codon eight hundred and ninety-seven (897) diagnostic of tuberous sclerosis-1. Curiously in this case no other clinical and neuroimaging findings specific for tuberous sclerosis were found.

Case 5

A 4-year-old girl born without consanguinity to a 34-year-old mother by normal vaginal delivery presented with increased behavioural issues in the form of temper tantrums, irritability, mood swings, grimace and reduced social interaction. Mother has noticed the changes starting during lockdown period during which child had increased screen time. On examination she responds to her name and she identifies family members. Blood investigations were done and revealed no abnormalities. EEG done was normal. She was placed in a playschool and started on speech therapy and considerable improvement was noted after 3 months with increased mingling and improved sitting tolerance. Parents were counselled for a genetic study and genetic report obtained. It revealed heterozygous missense variation in exon 3 and exon 7 of MED 13 gene and heterozygous missense variation in exon 32 of STAG 1 gene. Both genes were diagnostic of intellectual developmental disorder.

Case 6

Last case being four-year-old girl born out of non consaguineous marriage presented with clinical indications of speech regression since two years of age. Child had a normal birth history and attaining of milestones till two years of age followed by regression of speech. Other domains were normal for age. There is no history of seizures. Family history is unremarkabale except a mild speech delay in father. On examination she was very restless and inattentive, hyperactive, jargon speech present. Opthalmology, auditory testing and EEG were normal. MRI Brain done was normal. Whole exome sequencing was done which revealed a heterozygous missense variation in exon five of the ASH1L gene resulting in substitution of tyrosine for aspartic acid at codon 1756 diagnostic of mental retardation-52 and a heterozygous 5’ splice site variation in intron 54 of the ABCA13 gene-mutation of ABCA13 gene which has previously been reported to be the associated with the ASD.

In the last two cases early intervention helped the children and they were initially considered as virtual autism due to excessive screen time and very restricted social activity during COVID pandemic until when genetic variations were discovered.

Table 1: Table of summary.

Case no.	Age/ gender	Consasn-guinity	Other features	Para-clinical findings	Genetic test	Diagnosis	Comments
1	3 years/ F	No	Insomnia, motor delay, language regression, seizures	EEG: Epileptiform abnormalities	Heterozygous nonsense variation in exon 3 of MECP gene	RETT syndrome	-
2 and 3	6 years /twins /F	No	Dysmorphism, severe obsessive lips smacking and finger fidgeting, hyper extensibility of fingers, ACHD (ASD) recurrent respiratory tract infections	1st twin: Hypocalcemia 2nd twin: Video EEG: Generalised epileptiform activity	22q11.21 Consaguinity gene deletion in twins	Di George syndrome	Family denied diagnosis and specific Interventions, until a genetic aetiology was identified.
4	2 years/ F	Yes	Severe hypo-tonia, global developmental delay, seizures	EEG: Abnormal MRI Brain: Normal	Heterogeneous missense variation in exon21 of TSC gene	Tuberous sclerosis 1	No other clinical, neuroimaging findings specific for tuberous sclerosis.
5	4 years/ F	No	Behavioural issues	MRI Brain: Normal	Heterozygous missense variationin exon 3 and 7 ofMED13 gene andexon 32 of STAG1 gene	Intellectual developmental disorder	Early intervention helped this child and was initially considered as virtual autism, until when genetic variations were discovered.
6	4 years/ F	No	Speech regression	EEG: Abnormal MRI Brain: Normal	Heterozygous missense variation in exon 5 of ASH1L gene mutation of ABCA13 gene	Mental retardation ASD	-

DISCUSSION

In the recent years we have seen a shift from understanding general concepts of genetic risk to giving more specific attention to a large number of heterogeneous, individual genetic variants associated with ASD risk. About 71 studies were published over the past 10 years which indicates a global autism prevalence of 100/10,000. The male-to-female ratio was 4.2 and percentage of autism cases with co-occurring intellectual disability was 33.0%.[2] A meta-analysis published in 2016 reported that 74-93% of ASD risk is heritable.[6] Sibling studies indicate that ASD occurs in 7-20% of subsequent children after an older child is diagnosed with ASD.[7,8] Several genetic diseases are related with an increased risk of ASDs, being responsible for 5-10% of total diagnosed cases. The first evidence for specific genetic risk factors in ASD arose in rare genetic syndromes, such as fragile X syndrome and tuberous sclerosis.[9,10]

With the advancement of Next Generation Sequencing, if the genetic aetiology is identified in the children who present as ASD in early years, it can help in better acceptance of the diagnosis by the family and counselling family on the prognosis and motivating for interventions. Children with genetic disorders associated with autism can develop potentially life-threatening medical illness that arise secondary to their genetic condition. Hence it is important to provide genetic counselling for the family and to screen for associations, even before they clinically emerge. Examples are congenital heart disease in Williams syndrome, epilepsy in tuberous sclerosis and

Cornelia De Lange syndrome, and metabolic defects in PKU. Prompt diagnosis of these problems are often helpful in developing specialized interventions. This can maximize benefits derived from non-medical, academic, or psychological interventions as well as prevent medical deterioration from occurring.

CONCLUSION

Whole exome or whole-genome sequencing for children could soon become the standard of care for ASD in some countries and it is desirable to refer children with specific genomic findings to a clinical geneticist. Though intervention would mostly remain the same, genetic aetiology helped us in prognosticating and improved the family's outlook towards the disease.

Hence it is desirable to identify genetic variations in all possible ASD cases as it has the potential to improve family planning, trigger screening for co-occurring medical problems, aid the prognosis, and start specific interventions.

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