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AUTISM SPECTRUM DISORDER AND GENETIC ASSOCIATIONS IN A TERTIARY PRIVATE HOSPITAL IN NORTHERN MEXICO

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ABSTRACT

Background: Autism spectrum disorder (ASD) consists of a group of heterogeneous genetic neurobehavioral disorders associated with developmental impairments in social communication skills and stereotypic, rigid or repetitive behaviors. **Aims:** To review behavioral, psychiatric and genetic associations related to ASD. **Methods:** Descriptive, prospective, observational and longitudinal study. Inclusion criteria were patients with ASD from July 2022-July 2023 in a tertiary private hospital. Study variables were age, gender, clinical features, level of autism, type of epilepsy, comorbidities, genetic syndromes, epileptic syndromes and type of treatment. Information was captured in Excel and analyzed in SPSS. **Results:** We review 36 patients with ASD from July 2022-July 2023. Age: 2-31, 10±24.7. Clinical features: self -injurious behaviors 40%, aggression 35%, sleep disorders 25%. Levels of autism 1 (17- 47.2%), 2 (12- 33.3%) and 3 (7- 19.4%). Comorbidities 27 (75%): intellectual disability 15 (41.6%), attention deficit hyperactivity disorder (ADHD) 2 (5.5%), Tourette's syndrome 1 (2.7%), global developmental delay 3 (8.3%), developmental language disorder 4 (11.1%), cerebral palsy 1 (2.7%), migraine 1 (2.7%). Genetic syndromes 12 (33.3%): Prader Willli, Angelman, Lafora, Down, Noonan, Usher, fragile X, lissencephaly, callosum corpus dysgenesia, neurofibromatosis, tuberous sclerosis, Type II Chiari malformation. Epileptics syndromes 4 (11.1%): West 1 (2.7%), Lennox Gastaut 1 (2.7%), atypical absences 2 (5.5%). Association was found between severe autism and genetic syndromes with statistical significance ($p<0.05$). **Conclusion:** Autism characteristics in genetic syndromes demand attention across time and circumstance, to evidence and support related changes in need.

KEYWORDS : autism, genetic syndromes, behaviors.

INTRODUCTION:

Autism spectrum disorder (ASD) consists of a group of heterogeneous genetic neurobehavioral disorders associated with developmental impairments in social communication skills and stereotypic, rigid or repetitive behaviors.

Rating or assessment scales that have been validated for both clinical and research purposes are helpful in establishing the diagnosis of autism. These scales include the Autism Diagnostic Interview-Revised (ADI-R)[1] and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)[2]. ASD affects between 1 to 2% of children with 4:1 male-to-female ratio and a heritability estimate between 70 and 90%.

The concept of "syndromic autism" (ASD associated with morphological signs or symptoms helpful in the identification of specific genetic disorders) stands in contrast to "non-syndromic autism" (idiopathic ASD with no associated signs or symptoms).The etiology of ASD involves a complex interplay between inheritance and environmental factors influenced by epigenetics.

The cause of ASD is heterogenous involving genetics with multiple different gene variants and environmental influences triggering physiological changes in genetically sensitive individuals along with in utero and metabolic factors including mitochondria dysfunction reported in 10 to 20% of patients with ASD.

Familial and heritability studies have shown that genetic factors contribute, with estimates as high as 90% with tuberous sclerosis, fragile X, and Rett syndromes as examples of single gene conditions found but accounting for less than 10% of all ASD cases.

Genetic syndromes and chromosome findings where autism is a recognized feature are[3,4:]

Table 1. Genetic syndromes in autism

- Adenylate succinase deficiency - Angelman and Prader-Willi syndromes (AS–maternal or PWS–paternal 15q11-q13 deletions)	-Smith-Lemli-Opitz syndrome -Down syndrome
-Apert syndrome -Noonan syndrome	-Smith-Magenis syndrome (17p11.2 deletion) -Duchenne muscular dystrophy
-15q11.2 BP1-BP2 microdeletion (Burnside-Butler) syndrome -Oculo-auriculo-vertebral spectrum	-Sotos syndrome -Fragile X syndrome (FMR1 gene)
-CHARGE syndrome -Phelan-McDermid syndrome (22q13 deletion)	-Tuberous sclerosis -Hypomelanosis of Ito
-Chromosome 15 duplications (maternal origin) -PTEN gene associated disorders with extreme macrocephaly (Cowden/Bannayan-Riley-Ruvalcaba syndrome)	-Turner syndrome -Joubert syndrome
-Chromosome 16p11.2 deletions -Rett syndrome (MECP2 gene)	-Untreated or poorly treated phenylketonuria (PKU) -Mitochondrial dysfunction
-Cohen syndrome -Shprinzten/velo-cardio-facial/DiGeorge, (22q11 deletion)	-Williams syndrome -Moebius sequence
-De Lange syndrome	

Genetic testing often begins with chromosomal microarray analysis to identify copy number variants to search for a cause of autism spectrum disorder and other related conditions.

While the etiology of ASD is complex, it involves genetic factors with 800 genes recognized, accounting for 4% of all human genes that are implicated in ASD.

Behavioral and psychiatric comorbidities are common in individuals on the autism spectrum, and can have a substantial impact on overall health, quality of life, and long-term prognosis.

Approximately 30% of individuals with ASD require psychological and psychiatric treatments including medication for behavioral problems including hyperactivity, impulsivity, inattention, aggression, property destruction, self-injury, mood disorders, and psychotic or tic disorders.

Early intensive behavioral intervention is a well-established treatment for young children with ASD and is based on the principles of applied behavior analysis.

For the treatment of irritability associated with ASD, the antipsychotics risperidone and aripiprazole are licensed and approved by the US Food and Drug Administration[5].

Stimulant medications are considered first line agents for attention deficit hyperactivity disorder (ADHD) in individuals with ASD, given that overall they are most often effective and generally well tolerated compared to other ADHD medications. The RUPP research team and later Reichow et al.[6] demonstrated a clear superiority of methylphenidate over placebo in children with pervasive developmental disorder.

Regarding non-stimulant medications for ADHD in ASD, both atomoxetine and alpha-2 agonists have shown benefit. Harfterkamp et al.[7], in a double-blind treatment trial of patients age 6 to 17 years with ADHD and ASD using atomoxetine 1.2 mg/kg/day or placebo for eight weeks, found that atomoxetine moderately improved ADHD symptoms, but with frequent adverse events including nausea, decreased appetite, fatigue, and early morning awakening.

Fluoxetine has been shown to improve repetitive behaviours in adults with ASD.

Exogenous melatonin (available as an over-the-counter supplement) in both immediate-release and extended-release formulations, has been shown to be safe and effective in improving sleep patterns in children with ASD[8].

The objective was to review behavioral, psychiatric and genetic associations related to ASD.

METHODS:

Descriptive, prospective, observational and longitudinal study.

Inclusion criteria were patients with ASD from July 2022-July 2023 in a tertiary private hospital.

Exclusion criteria were files with incomplete data.

Data were obtained from clinical records.

Study variables were age, gender, clinical features, level of autism, type of epilepsy, comorbidities, genetic syndromes, epileptic syndromes and type of treatment.

Level one of ASD is seen as the mildest level of ASD, and it is often referred to as "high functioning". Children need some degree of support based on their degree of impairment related to social communication and restricted or repetitive behaviours. They struggle with conversation, eye contact, reading body language etc.

Level two is likely to require "substantial support" based on their social communication abilities and their restricted or repetitive behaviours. They struggle with non-verbal forms of communication, along with sensory issues, focus on routines and fixation on objects or topics.

Level three requires 'very substantial support," It might be a child who has severe deficits in verbal and nonverbal communication. They will have very limited speech and communication, limited social initiation, and respond only to the most direct social cues. They will often have an intellectual disability which makes it harder for them to learn new skills. They may be so driven by their restricted or repetitive behaviours that they are unable to function effectively in different settings.

We studied whether there is an association between severe autism (level three) and genetic syndromes.

Information was captured in Excel.Tests (measures of central tendency: mean, median, average, standard deviation, chi-squared test) were applied in the SPSS program.

RESULTS:

We review 36 patients with ASD from July 2022-July 2023. Age: 2-31, 10±24.7. Gender: male 61.1%. Perinatal asphyxia 7 (19.4%). Clinical features: self -injurious behaviors 40%, aggression 35%, sleep disorders 25%. Levels of autism 1 (17-47.2%), 2 (12- 33.3%) and 3 (7- 19.4%). Focal epilepsy 22 (61.1%). Comorbidities 27 (75%): intellectual disability (ID) 15 (41.6%), attention deficit hyperactivity disorder (ADHD) 2 (5.5%), Tourette's syndrome 1 (2.7%), global developmental delay 3 (8.3%), developmental language disorder 4 (11.1%), cerebral palsy 1 (2.7%), migraine 1 (2.7%). Genetic syndromes 12 (33.3%): Prader Willli, Angelman, Lafora, Down, Noonan, Usher, fragile X, *lissencephaly,* callosum corpus *dysgenesia, neurofibromatosis, tuberous sclerosis,* Type II Chiari malformation. Epileptics syndromes 4 (11.1%): West 1 (2.7%), Lennox Gastaut 1 (2.7%), atypical absences 2 (5.5%). Non-pharmacological treatment (speech, behavioral and sensory therapy): 25 (69.4%). Pharmacological treatment cannabidiol and antiseizure drugs: 33%.

Association was found between severe autism (level three) and genetic syndromes with statistical significance ($p<0.05$).

DISCUSSION:

Research over recent years has indicated significantly elevated rates of autism and related characteristics in several genetic syndromes associated with intellectual disability.

Prevalence estimates within the general population indicate rates of autism of at least 1%. However, people with a genetic syndrome associated with ID are reported to be at least ten times more likely to show autism characteristics than the general population.

Some syndrome groups evidence a profile of characteristics which includes significant repetitive behaviours and/or interests (RRBIs) alongside differences in social communication that are similar to that of autistic people who do not have a genetic syndrome, combined with comparatively heightened social motivation (e.g. Rubinstein-Taybi syndrome[9], Sturge-Weber syndrome[10]).

For other syndromes, both social interaction and communication differences evidence similarities with non-syndromic autism, while RRBIs may be less apparent in the

syndrome or may present differently to those described in autistic people without a syndrome (e.g., Phelan-McDermid syndrome[11], Sotos[12]).

On the Autism Diagnostic Observational Schedule (ADOS), increased repetitive speech, stereotyped behaviours, and hyperarousal are reported to distinguish those with Fragile X Syndrome from non-syndromic autism[13].

Social anxiety distinguishes those with Cornelia de Lange Syndrome from non-syndromic autism[14,15] and is positively associated with the prevalence of autism characteristics across the lifespan, independent of Iq[16].

Using the ADOS, estimates of autism in William Syndrome (WS) range from 30 to 35%, although some behaviours may be better characterised as part of WS, for example, difficulties with imagination/creativity, gesture, and repetitive behaviours, rather than indicative of an additional autism diagnosis[17]. Hypersociability is considered to be central to the WS phenotype[18], alongside auditory hypersensitivity[19] and repetitive behaviours[20]. People with WS also experience significant anxiety, which increases with age and results in lower social motivation.

Strong interests described as 'intense obsessionality' are more marked in Prader-Willi Syndrome than non-syndromic autism.

People with Angelman Syndrome present with fewer autism characteristics compared to those with PWS, particularly within the domain of social affect, such as increased shared enjoyment of social interactions[21].

A 'friendly stereotype'—that individuals are overly sociable—is also associated with Down Syndrome. The prevalence of co-occurring autism in DS is estimated to be 16–41%. The majority of people with DS who score highly on the SCQ[22] and ADOS-2 have more severe ID than individuals with DS alone.

The behavioural phenotype of Smith Magenis Syndrome includes sleep disturbances, self-injurious and maladaptive behaviours, stereotypies, and sensory difficulties[23].

Epilepsy is the most common feature of Tuberous Sclerosis Complex and has been identified as related to autism characteristics[24]. Seizure onset before age 1 year and greater severity of infantile spasms are positively correlated with autism characteristics[25].

In our study, we found association between severe autism (level three) and genetic syndromes, which agrees with what is reported in the literature.

CONCLUSIONS:

The behavioural heterogeneity of autism-related behaviours within and across genetic syndromes indicate some degree of syndrome specificity.

Autism characteristics in genetic syndromes demand attention across time and circumstance, to evidence and support related changes in need.

Conflict of interest:

The authors declare no conflicts of interest.

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