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AUTS-2 Syndrome. Gravity comparison of three cases: a case series and review of the literature

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Introduction: Haploinssufficiency of AUTS2 gene has been associated with a syndromic form of neurodevelopmental delay called AUTS2 Syndrome (AUTS2S). It is characterized for having attention/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), mild global development delay (GDD) and intellectual disability (ID). Clinicians also reported microcephaly, feeding difficulties, generalized hypotonia and ptosis.Due to its great variability, the AUTS2 Syndrome Severity Scoring System (ASSS) was established to assess the severity of the syndrome presentation. It is based on 32 characteristics including items of growth, feeding, neurodevelopment and congenital anomalies.
At the molecular level, the AUTS2 gene consists of 19 exons that are divided into a non-conserved N-terminal region and a conserved 3' terminal end. There is a short isoform expressed primarily in the brain that initiates at an alternative transcription site and includes the last 11 exons. Variants that disrupt this final part of the gene have been associated with a severe phenotype.
Objectives: To describe and compare 3 patients affected with AUTS2 syndrome using the ASSS.
Methods: (1) Case series: Comparison of the patients diagnosed with AUTS2 Syndrome using the AUTS2 Syndrome Severity Score. (2) Narrative review of the AUTS2 syndrome and the genotype-phenotype correlation through PubMed database (1990-2020). Key terms: "*AUTS2*", "AUTS2 syndrome", "ADHD", "neurodevelopmental disorder", "autism".
Results: 1 (ASSS score: 12). Interstitial duplication long arm of chromosome 7. Characteristics: microcephaly, GDD, ASD features, ADHD, auditory hypersensitivity. Finger flexion and syndactylia, arched eyebrows, palpebral fissures, epicanthus, nares, micrognathia, narrow mouth.
2 (ASSS score: 13). Pathogenic variant exon 9. Characteristics: GDD, feeding problems, ID, ASD features, auditory hypersensitivity, ADHD, hypotonia, cerebral anomalies, hypertelorism, anteverted nostrils, broad nasal bridge, micrognathia, low-set ears, narrow mouth.
3 (ASSS score: 13). Pathogenic variant exon 16. Characteristics: ID, short stature, feeding problems, auditory hypersensitivity, ADHD, hypotonia, umbilical hernia, hypertelorism, proptosis, short palpebral fissures, epicanthus, prominent nasal tip, anteverted nares, low-set ears.
Conclusions: Currently, 65 patients with pathogenic variants in AUTS2 are described in the literature. Significantly higher ASSS values have been found in patients with pathogenic variants affecting the 3' end of the gene. Further research is needed, since genetic diagnosis of affected patients contributes to improved clinical protocols and personalized treatment.

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Autism spectrum disorder and genetic: a possible correlation?

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Introduction: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in social interaction and communication, whose etiology is heterogeneous, including genetic, epigenetic, and environmental factors. It is associated with restricted interests and stereotyped behaviors with high prevalence rates in general population, neurobiological bases and high heritability.
Objectives: The aim of our study is to identify the possible phenotype-genotype relationships regarding neurodevelopmental disorders and to evaluate a correlation between genomic alterations and the manifestations of the overt and subthreshold ASD in a family administered psychiatric clinical evaluations at our hospital.
Methods: The family M underwent a psychiatric evaluation through the MINI interview according to the SCID-5 criteria, the AQ, ADAS, PAS-SR, SHI-SHY,SHY-OBS to assess respectively the subthreshold traits of ASD in adulthood, the panic-agoraphobic, social-phobic and obsessive-compulsive spectrum and CAT-Q Italian version, to evaluate social camouflage behaviors typical of ASD individuals. Array Comparative Genomic Hybridization was used for studying DNA imbalances in this family.
Results: We found that Mrs.A, her father, her brothers and her older sister had a microduplication, very likely pathogenic, since it has been never reported in healthy subjects and harbors several genes. It could be related with overt and subthreshold traits of ASD. From the questionnaires administered and from the clinical interview, it emerged that Mrs.A is affected by ASD and Bipolar Disorder. Her twin brothers have been evaluated at early ages by child neuropsychiatric clinic and they were diagnosed with ASD and mental and psychomotor impairment. Her father was reported a significant trend in ADAS, AQ, PAS-SR, SHI-SHY and SHY-OBS scores. Finally, about her older sister, even if our results were not significant for an ASD diagnosis, we speculated that she performed a high score in some ADAS items and in the CAT-Q but not in the AQ. Females generally tend to attract fewer attention than males thanks to their better coping and camouflaging mechanisms as well as their ability to "disappear" in large groups.
Conclusions: Genetic knowledge can have a relevant clinical impact; a genetic etiology can be identified in individuals with ASD, leading to the identification of treatable psychiatric comorbidities. Furthermore, knowing the causative genetic variants of ASD could provide crucial information for genetic counseling as well as to understand the neurobiology of these disorders and to contribute to an early diagnosis.

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