

The Association between Apert Syndrome and Autistic Spectrum Disorder in a Patient of Cypriot Heritage

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Apert syndrome (AS) is the most frequent form of the acrocephalosyndactyly syndromes. It has an estimated incidence of one in 100000 to 160000 newborns. A 3-year-old boy with the karyotype of 46, XY and diagnosed with AS was directed to our clinic for delay in speech acquisition. This is the first case of AS in the Cyprus Island. Due to the mutation in fibroblast growth factor receptor 2 (FGFR2) gene, he was born with the typical phenotype of AS. The Ankara Developmental Screening Inventory (ADSI) was applied to the parents, and the patient was asked some practical directives. The outcome of ADSI showed that the child could be at 13-15 months of developmental age with more than 30% of growth retardation. As per our knowledge, this is the second case of 46, XY child who was diagnosed with acrocephalosyndactyly syndrome and shows a strong association with autistic spectrum disorders.

Keywords: Apert syndrome, autistic spectrum disorder, autism spectrum disorders, Cyprus

INTRODUCTION

The human brain is the outcome of numerous evolutionary processes, and the same mechanism is likely to be involved in the pathogenesis of mental illnesses (1, 2). A negative selection of the risk alleles shows predisposition to mental illnesses, and it is clearly shown in the phenotypes in the society (3). Thus, psychiatric disorders have a strong association with rare and *de novo* mutations (4). However, mostly polygenic predispositions are seen in these disorders (5). Particularly, genetic studies have indicated that common psychiatric disorders are highly polygenic (6, 7). Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders that are generally highly heritable and show significant heterogeneity in genetics, phenotypes, clinical presentation, and associated comorbidities (8). Several common and rare genetic variants are known till date, which have an association with ASD (9). Apert syndrome (AS) is a rare congenital condition with an estimated incidence of 1/100000 to 1/160000 newborns (10). This condition is characterized by craniosynostosis, mid-facial malformations, and complex symmetrical malformations of the hands and feet (11).

Craniofacial deformities, acrocephaly (cone-shaped calvarium), prominent forehead, proptosis, hypertelorism, and flattened nose with a low bridge are the main clinical manifestations of AS. Oral signs might include pseudocleft, high-arched palate, transverse, and sagittal maxillary hypoplasia, dental crowding, delay in dentition, ectopic teeth, disarrayed teeth, and teeth crowding. Rarely, clinical symptoms related to the central nervous system and the cardiac, gastrointestinal, and urogenital system are noted (12). The mandible is generally normal in size; however, pseudoprognathism can be seen. Several vertebral anomalies have been reported (12, 13).

The mutations within the fibroblast growth factor receptor-2 (*FGFR2*) gene on 10q26 locus develop autosomal dominant AS. The *FGFR2* gene encodes the protein responsible for blood vessel formation; wound healing; embryonic evolution; and regulation of cellular division, growth, and maturation with three other FGFRs (13). Additionally, FGFR binds to fibroblast growth factors and plays a significant role in the fusion process of the skull bones (14).

Heterozygosity for 1 of 2 mutation in the exon 7 of the *FGFR2* gene causes AS: S252W and P253R (14, 15). Only two patients had an Alu-element insertion in or near the exon 9 (15). Park et al. (16) reported that there are no statistically significant clinical differences between the 2 major mutations (16). In contrast, Slaney et al. (17) indicated differential effects

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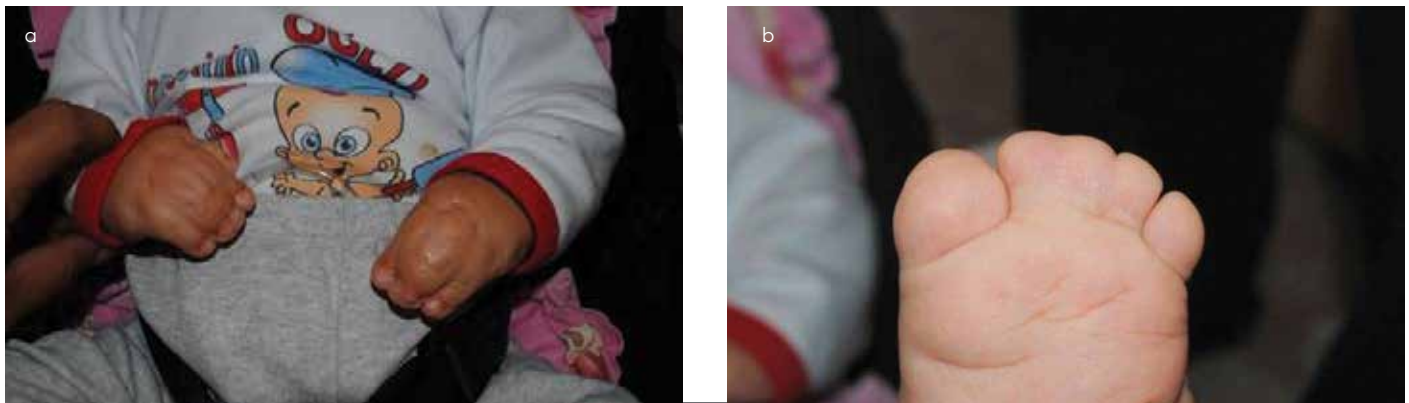


FIGURE I. a, b. (a) Apert type II hand complete syndactyly and partly syndactyly foot before his surgery, (b) apert type II hand partly syndactyly foot before his surgery

of the 2 *FGFR2* mutations on syndactyly and cleft palate in AS (17). Syndactyly in both the hands and feet was more severe in patients with the P253R mutation. In contrast, cleft palate was significantly more common in patients with the S252W mutation. No significant differences were found in the prevalence of other malformations associated with AS (17).

Mental retardation is clearly associated with AS in some cases and it is believed that the central nervous system malformations are responsible (18). There are only few articles mentioning a possible association between acrocephalossyndactyly syndromes and developmental delay. In addition, Morey-Cannellas et al. (18) published the first case of a child with AS showing ASD. Herein, we present a 3-year-old boy diagnosed with AS, and we aimed to show a strong association with ASD.

CASE PRESENTATION

A three-year-old boy with the karyotype of 46, XY and diagnosed with AS was directed to our clinic for delay in speech acquisition. This child is the first case of AS in the Cyprus Island.

During clinical assessment, the child was distracted, had increased psychomotor activity, and was avoiding eye contact and social contact; also, he had absence of verbal and non-verbal communication skills and did even use any gestures. He preferred playing alone and could not respond to his name.

The Ankara Developmental Screening Inventory (ADSI), which is the program analyzing the developmental age and mental capability of children aged 0-6 years, was applied to his parents and the child was asked some practical directives (19).

The outcome of ADSI showed that the child could be at 13-15 months of developmental age with more than 30% of growth retardation.

For further analysis, consent forms were provided by the parents, and the medical ethics committee approved the study. A heterozygote P253R mutation within the *FGFR2* gene has been detected by a molecular genetic test. The patient was born with the typical phenotype of AS patients, such as craniosynostosis and type II syndactyly (Figure I, b), bulging and wide-set eyes, and tongue thrust (anterior open-bite) and an underdeveloped upper jaw, mid-facial growth deficiency, and class III malocclu-

sion. Before presenting to our clinic, he had five different surgeries in Turkey and Cyprus at the several hospitals to normalize his life and for survival.

DISCUSSION

As far as we present the case of a child who was diagnosed with acrocephalosyndactyly syndromes and show strong association with ASDs. Since 2003, there has been no case reported with AS and showing ASD.

Autism is an example of a disorder that is more difficult to diagnose, as it is an abnormal behavioral pattern (20). The diagnosis of ASD requires a comprehensive assessment, including (i) a detailed developmental history, (ii) clinical observation/assessment, and (iii) obtaining wider contextual and functional information (20). The symptoms should also be assessed using scales, such as Autism behavior Checklist and Childhood autism rating scale (11).

The patient had to undergo five important surgeries at the early ages of life for normalizing his life and for survival. Therefore, he had long periods of hospitalization and, however his social ambience could be affected. This may lead to psychological problems of development, immature social interactions, isolation, and ostracism.

To date, the knowledge of association between ASD and acrocephalosyndactyly syndromes are still limited with only few examples (18).

CONCLUSION

We presented this case report with the aim that it will raise awareness of a possible association between acrocephalosyndactyly syndromes and ASDs. In the future, research should be conducted to screen a sample of acrocephalosyndactyly cases for ASDs for clarifying whether there is an association. If proven positive, then, a further study of such cases could help clarify the etiology of ASDs.

Informed Consent: Written informed consent was obtained from parents of the patient who participated in this study.

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