Autism spectrum disorder and achondroplasia in an Egyptian patient

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Received 04 April 2021
Revised 30 November 2021
Accepted 03 December 2021
Published 08 June 2022

Middle East Journal of Medical Genetics
2022,2:101–104

Autism spectrum disorder (ASD) and achondroplasia are two distinctive disorders. Co-occurrence of ASD with different monogenic disorders, chromosomal aberration, and molecular defined syndromes has been reported. Yet, the coexistence of ASD with achondroplasia has been recently reported; it was supposed to be merely coincidental. It is of particular interest herein to report on an Egyptian patient having achondroplasia and ASD simultaneously. The current report includes a comparison of both cases and throws light on the importance of genetic and environmental contributions in the etiology of ASD.

Keywords:
achondroplasia, autism, epilepsy, FGFR3

Middle East J Med Genet 2:101–104

2090-8571

Introduction

Achondroplasia is the most common form of short-limbed dwarfism. The condition occurs in one in 15 000 to 40 000 newborns (Ireland *et al.*, 2012a, 2012b). Achondroplasia is inherited in an autosomal dominant pattern. The problem in achondroplasia is a defect in the process of ossification, which converts cartilage to bone, particularly in the long bones of the arms and legs. Achondroplasia results from mutations in *FGFR3* gene and is characterized by disproportionate dwarfism in the form of short upper arms and thighs. There is limitation in the range of motion at the elbows. There is macrocephaly with prominent forehead. Fingers are typically short, and the ring and middle fingers may diverge, giving the hand a three-pronged (trident) appearance. People with achondroplasia are generally of normal intelligence. Mutations in ~80% of these cases result from new mutations in the *FGFR3* gene (Lainhart *et al.*, 1997).

Autism spectrum disorder (ASD) is a neurodevelopmental disorder. Its diagnosis is based mainly on a triad of impaired social interaction and difficulty interacting appropriately with people, impaired communication, restricted interests, and repetitive behaviors. Fernandez and Scherer (2017), categorized ASD into three groups: (a) clinically defined syndromes accounting for 4–5% of ASD cases including chromosomal aberrations like trisomy 21, monogenic syndromes like neurofibromatosis 1, tuberous sclerosis complex, and microdeletion syndromes like Phelan McDermid (22q13 deletion) syndrome; (b) molecularly defined ASD syndromes, where patients are not easily identified clinically, accounting for ~20% of the cases, for example, iso-dicentric 15q; and (c) ASD-risk genes, for example, *ADNP*, *ARID1B*, *ANK2*, *SCN2A*, and ASD, associated copy number variations, for example, 16p11.2 deletion/duplication, and unidentified group, representing ~75% of cases.

Co-occurrence of ASD with different rare syndromes was previously reported and rarely replicated, Sertçelik *et al.* (2016), reported a child with Kabuki syndrome and ASD. Co-occurrence of Gomez-Lopez-Hernandez syndrome and ASD was reported by Kotetishvili *et al.* (2018). Therefore, the coexistence of ASD and certain syndromes may help to shed light on the genetic basis of ASD. Co-occurrence of ASD with achondroplasia was first reported by Dy and Tanchanco (2019). Herein, we report a second case of an Egyptian patient with achondroplasia and ASD.

Clinical report

A male patient, 1 year and 10 months was presented to our department owing to short stature and macrocephaly in 2015. He is an offspring of nonconsanguineous parents who are apparently normal. The mother and father were 32 and 35 years old, respectively, at the time of his birth. He has a younger apparently normal brother. His mother received progesterone from the second month of pregnancy till delivery. The delivery was at 33 weeks of gestation because of premature uterine contractions by cesarean section. Cyanosis was

noted after birth. He was put under observation for 2 h and was discharged after improvement. Short limb and macrocephaly were noted after birth. The patient had delayed milestones of development.

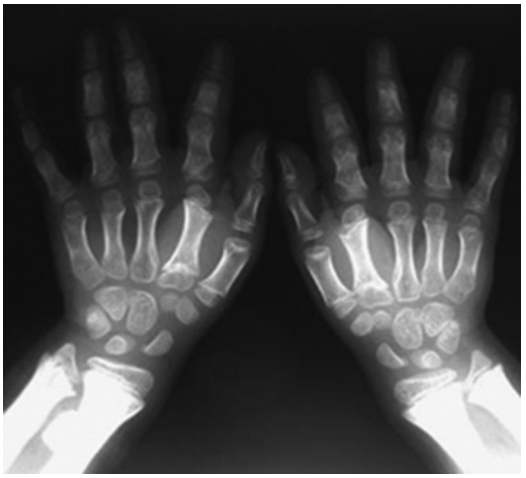
On examination, the patient had frontal bossing, depressed nasal bridge, broad upturned nostrils, upward slanting of palpebral fissure, long philtrum, tented thin upper lip, low-set cupped ears, short neck, upper limbs were short particularly rhizomelic, trident hand, short rhizomelic lower limb, and brachydactyly of the toes. Anthropometric measurement showed his weight was 9 kg (−2.4 SD), head circumference was 51.5 cm (+1.65 SD), and his length was 69 cm (−5.2 SD). The diagnosis of achondroplasia was based on clinical and radiological findings, and it was confirmed by molecular analysis of *FGFR3* gene by direct sequencing, which revealed a heterozygous missense mutation at nucleotide c.1138 G>A, leading to arginine substitution for glycine at codon 380, which is the most common mutation in achondroplasia. When the patient was 5 years and 7 months, his mother was referred again to our department complaining of delayed speech, severe attention deficit, diminished response to his name, absent eye contact, and abnormal repetitive behavior. The patient also had three attacks of fainting and loss of consciousness. He met the diagnostic criteria of ASD, and CARS test was provided, showing severe autistic behavior. Electroencephalograms (EEG) showed focal left fronto-temporal epileptogenic dysfunction. Social quotient and social age were evaluated using the Vineland Social Maturity Scale, showing 47 (moderate social delay) and 2.6 years, respectively. MRI for the brain showed mild cortical and central brain atrophy (Figs. 1 and 2).

Discussion

Autism is a behavioral disorder, and its diagnosis depends mainly on clinical history. There are no diagnostic biomarkers, and it is etiologically and biologically heterogeneous (Lidia *et al.*, 2014). Several reports focused on the genetic contributions to the etiological factors that may increase the susceptibility to environmental factors for autism (Moss and Howlin, 2009; Piggot *et al.*, 2009). To date, genetic studies did not identify specific genes of strong effect on autism, but researchers are directed toward genetic complexity at the neurological level as a cause of autism. It is well known that autism is associated with known genetic syndromes, for example, fragile X syndrome (Kau *et al.*, 2004) and tuberous sclerosis (Jeste *et al.*, 2008). Therefore, several reports point toward genetic contributions to the mechanism that increases the susceptibility to environmental factors for autism (Abrahams and Geschwind, 2008). Herbet *et al.* (2006) identified 135 genes in overlapping regions related to autism (56 of these genes have never been studied before). Bioinformatics' approaches supported the role of these genes as environmentally responsive and favored describing autism as a multisystem disorder not specifically related to the nervous system (Herbet *et al.*, 2006). One of these genes is *FGFR3* (fibroblastic growth factor receptor 3), where its mutations cause achondroplasia and thanatophoric-dwarfism (Lainhart *et al.*, 1997).

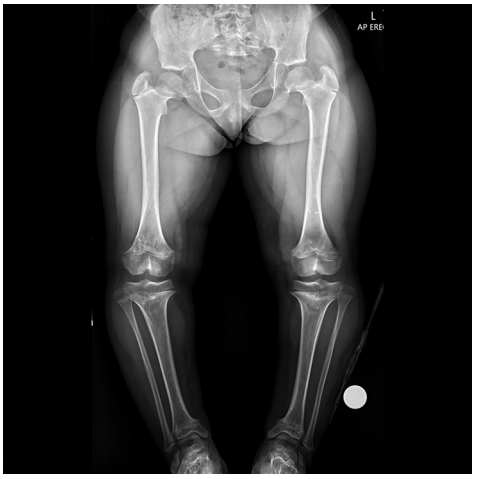
Achondroplasia is the most common cause of dwarfism in humans. It has a phenotypic presentation of disproportionate short stature and craniofacial and skeletal abnormalities (Ireland *et al.*, 2012a, 2012b). More than 97% of patients with achondroplasia have two mutations (G1138A and G1138C) in the *FGFR3* gene. Both achondroplasia and autism are two distinctive disorders, but still bioinformatics have the

Figure 1



Mild generalized shortening of metacarpals and phalanges. Note the divergence of the fingers from one another (trident hand).

Figure 2



Frontal view of the knees demonstrates relative broadened distal femoral and proximal tibial metaphysis, with narrowing of the femoral intercondylar notch. The femora and tibiae are short and broad, and the fibulae are relatively elongated.

probability based on the prevalence studies that two to five in 10 000 000 patients could have the susceptibility of having both syndromes simultaneously (Horbert *et al.*, 2006).

Dy and Tanchanco (2019), reported the first patient who showed both syndromes simultaneously. In 2015, our patient presented to our clinic at the age of 1 year and 10 months as a case of achondroplasia. He was diagnosed initially clinically and radiologically, and his diagnosis was confirmed by molecular analysis of *FGFR3* gene by direct sequencing, which revealed heterozygous missense mutation at nucleotide C1138G>A which is a common mutation in achondroplasia. On his second visit in 2018, he was 5 years and 7 months old, and his mother complained that her child has severe delayed speech, marked social impairment, and stereotyped repetitive behavior. Following his behavioral development and by subjecting him to the CARS test, he proved to have severe autistic behavior. Our patient was complicated by perinatal insult in the form of prematurity, cyanosis, followed by incubation after birth. Similar insult was reported in the case of Cheng Dy and Tanchanco, where their patient was admitted to the neonatal ICU because of hyperbilirubinemia and suspected sepsis. A comprehensive meta-analysis was done by Gardener *et al.* (2011), studying the perinatal and neonatal risk factors for autism, suggesting that exposure to a broad class of comorbid conditions may increase the risk for developing autism.

Epilepsy has never been reported in cases with achondroplasia. However, Okazaki *et al.* (2017), delineated epilepsy in a *FGFR3*-related disorder, in a patient with hypochondroplasia who had bilateral medial temporal lobe dysgenesis.

Recurrent fainting and EEG changes were reported in our patient and his MRI brain showed mild cortical and central brain atrophy. On the contrary, the occurrence of autism and epileptiform EEGs even in the absence of epilepsy have been reported as high as 60%. Some investigators propose that these abnormalities may play a causal role in the autism phenotype (Spence and Schneider, 2009).

Genetic analyses performed in the existence of specific genetic syndromes, such as achondroplasia, may provide opportunities for understanding the genetic etiology of ASD. Co-occurrence of ASD and certain genetic syndromes led researchers to believe that understanding pathways in genetic syndromes is helpful in determining the causes of ASD (Persico and Bourgeron, 2006).

The current report provides new evidence for the contribution of perinatal brain insult, as an environmental factor, and genetic interaction in the etiology of ASD. Our patient is the second case reported in the literature to have both ASD and achondroplasia simultaneously.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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