Case Report

Achondroplasia and Down Syndrome In An Infant: A Rare Co-Occurrence

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Abstract:

Background: Achondroplasia and Down syndrome are among the most common and most recognizable genetic disorders. However, the co-occurrence of these common conditions in the same patient is quite rare. Advanced paternal and maternal age is an established risk factor for achondroplasia and Down's syndrome, respectively. Achondroplasia and Down syndrome may be accompanied by various complications, some of which can be quite severe. **Aims**: We aim to describe the clinical, radiographic and genetic findings in an individual with achondroplasia and Down's syndrome. **Case Description**: The patient who was born to a 38-year-old healthy mother and a 47-year-old healthy father was first referred to our hospital at the age of 15 months with hypotonia and short stature. After initial assessment, she was diagnosed Down syndrome and achondroplasia. Chromosome analysis revealed 47,XX,+21, and FGFR3 DNA sequencing revealed a de novo pathogenic heterozygous mutation (c.1144 G>A) (p.Gly382Arg). In the follow-up, she had recurrent respiratory infections and severe myelopathy symptoms with general muscular hypotonia and increased deep tendon reflexes resulting from craniocervical junction stenosis. Surgical decompression was planned; however, it could not be performed due to the development of severe respiratory distress. Despite aggressive supportive care she died at the age of 2 years with acute respiratory distress syndrome and disseminated intravascular coagulation. **Conclusion**: Achondroplasia and Down's syndrome are individually relatively common conditions that are associated with advanced parental ages. However, the co-occurrence of these common conditions in the same patient is quite rare, and may affect the survival.

Key words: Achondroplasia, FGFR3, Down's syndrome, advanced parental age, trisomy 21

INTRODUCTION

Achondroplasia is the most common genetic disorder of the skeleton with a birth prevalence of 1/25,000 live births (1). It is characterized by decreased growth of the long bones and base of the cranium, which can lead to neurological complications and increased risk for premature death. Clinical and radiological features of achondroplasia are well-defined (2). In infancy hypotonia is typical, and acquisition of developmental motor milestones is often both aberrant in patern and delayed. Although craniocervical junction compression increases the risk of death in infancy, most individuals with achondroplasia have a normal life expectancy and intelligence is near normal. The molecular etiology of achondroplasia was revealed in 1994 with the aid of linkage analysis which is followed by candidate gene approach (3-8).

Down syndrome is by far the most common and best known of the chromosome disorders. It is the most common single genetic cause of intellectual disability. The avarage life expectancy for Down syndrome is over 50 years (9). The incidence of Down syndrome due to trisomy 21 conceptions increases strikingly with maternal

age. In 95% of cases the chromosomal basis for Down syndrome result from non-disjunction giving rise to trisomy 21. The rest of the cases are due to translocations, mosaicism and other chromosomal rearrangements. Conventional karyotyping is therefore essential to determine the genetic basis for Down syndrome. Congenital heart disease is a major factor in increased mortality in infancy and childhood (10). Down syndrome in association with various other chromosomal disorders including Klinefelter syndrome, Turner syndrome, and triple X have previously been reported and well defined. However, the co-occurrence of achondroplasia and Down syndrome in the same patient is quite rare. We report on an infant with achondroplasia and Down syndrome who died at the age of 2 years due to acute respiratory distress syndrome and disseminated intravascular coagulation.

CASE REPORT

The patient was a 15-month-old girl at the time of admission to our department. She was born after a full term pregnancy to healthy consanguineous parents by cesarean section because of fetal distress. The father was 47 years old and the mother was 38 years old at the time of her birth. She has two healthy elder brothers. The patient's birth weight was 2920 g (-0.96 SD) and birth length was 45 cm (-1.93 SD). Antenatal screening tests were non-revealing, however, rhizomelic shortening of long bones was detected by fetal ultrasonography after 20th weeks of gestation. She was hospitalized in the neonatal intensive care unit and put on mechanical ventilation for respiratory distress and respiratory support was required after discharge. She developed recurrent lower respiratory tract infections and was diagnosed with immune deficiency necessitating intravenous immunoglobulin treatment. On admission, she had a body length of 67 cm (-3.39 SD), a weight of 7800 g (-2.92 SD) and an occipito-frontal circumference of 46 cm (0.01 SD). The limbs were shortened disproportionately with an arm span of 57 cm. The physical examination revealed relative macrocephaly, a prominent forehead, epicanthal folds, upslanting palpebral fissures, depressed nasal root, brachydactyly, and single transverse palmar crease on both hands. She was noted to have peripheral facial paralysis. The facial features of the patient were highly suggestive of Down syndrome; therefore, a chromosome analysis was obtained revealing a 47,XX,+21 karyotype. Radiographic investigations showed rhizomelic shortening of long bones, metaphyseal dysplasia and trident pelvis (Fig. 1A). Cranial magnetic resonance imaging demonstrated stenosis of cranio-cervical junction and spinal cord compression and myelopathy (Fig. 1B). Furthermore, considering the skeletal features consistent with achondroplasia, FGFR3 sequence analysis was performed and a pathogenic heterozygous de novo mutation c.1144 G>A (p.Gly382Arg) was identified (Fig 1C). A renal ultrasonography showed bilateral hydronephrosis. Echocardiographic evaluation demonstrated a spontaneously closed ventricular septal defect and an atrial septal defect. In the follow-up the patient was diagnosed with obstructive sleep apnea and upper respiratory tract evaluation revealed a horseshoe epiglottis. She suffered from recurrent pneumonia and tracheostomy was performed beacuse of inadequate ventilation. She had myelopathy symptoms with general muscular hypotonia and increased deep tendon reflexes, resulting from craniocervical junction stenosis. Surgical decompression was considered, but could not be performed due to the development of respiratory distress. On her last admission, she presented with aspiration pneumonia and despite aggressive supportive care she died at the age of 2 years with acute respiratory distress syndrome and disseminated intravascular coagulation.

DISCUSSION

Achondroplasia and Down syndrome are two distinct disorders with different genetic etiologies. It is estimated that achondroplasia affects approximately 250,000 people worldwide (1). On the other hand, Down syndrome has an incidence of 1 in 850 live births (10). The co-occurrence of these common conditions in the same patient is quite rare. To the best of our knowledge six cases have been reported in the literature so far (11).

Majority of achondroplasia cases result from an autosomal dominant missense mutation (p.Gly380Arg) localized in the transmembrane domain of FGFR3, and nearly all mutations arise on the paternal chromosome. The paternal origin of achondroplasia mutations in FGFR3 correlates with advanced paternal age (12). The paternal origin of activating mutations in FGF receptors is attributed to positive selection and clonal expansion of spermatogonial stem cells with age. A phenomenon termed "selfish spermatagonial selection" occurs in the testes of men as they age which may be associated with an increased prevalence of pathogenic de novo mutations, particularly in FGFR2, FGFR3, HRAS, PTPN11 and RET genes, in the next generation (13, 14). The present patient had advanced paternal age which would explain the occurence of de novo FGFR3 mutation.

Achondroplasia may be associated with increased mortality within the first year of life from complications related to the craniocervical junction (8). Population based studies suggest that this mortality risk which is probably secondary to central apnea associated with damage to respiratory control centers (16) may be as high as 7.5% without assessment and intervention (15). Therefore patients may die unexpectedly during their first year of life because of brainstem compression or obstructive apnea. Narrowing of the foramen magnum causes compression of the brainstem at the craniocervical junction in about 10% of patients which results in an increased frequency of hypotonia, quadriparesis, failure to thrive, central apnea and sudden death. In the present case, the patient manifested not only obstructive sleep apnea but also signs of craniocervical junction compression. She had myelopathy symptoms with general muscular hypotonia and increased deep tendon reflexes requiring surgical decompression. However, surgical decompression was not possible beceause of the development of respiratory distress and respiratory failure necessitating tracheotomy.

Down syndrome was first described by an English physician John Langdon Down in 1866, but its association with chromosome 21 could be established almost 100 years later by Dr. Jerome Lejeune in Paris (17). Down syndrome is the single most common genetic cause of intellectual disability and the extra copy of chromosome 21 is associated with Down's syndrome. In 95% of cases the chromosomal basis for Down syndrome results from non-disjunction giving rise to trisomy 21. However, Robertsonian translocation (2%), mosaicism (2%) and a variety of chromosome rearrangements (1%) may also be the basis of the disorder.. The incidence of Down syndrome increases with advance in maternal age.

Down syndrome is characterized by hypotonia, short stature, loose skin on the nape of the neck,, single palmar crease, clinodactyly, and various organ system malformations including congenital heart disease. In addition it is associated with an increased risk for leukemia and premature dementia (10).

The association of occipitoatlantoaxial instability with Down syndrome has previously been defined, and about 15% of individuals with Down syndrome have an atlanto-odontoid distance of 5 mm or greater and this is not seen in the general population (10). A small minority of individuals with Down's syndrome will develop neurological complications of atlantoaxial instability, and even a smaller number will suffer a catastrophic event in the absence of some earlier neurological signs (10). The present patient had advanced maternal age and the karyotype was 47,XX,+21. The co-occurrence of achondroplasia and Down syndrome in this patient probably further complicated the clinical course. She had severe hypotonia leading to aspiration pneumonia, and subsequent respiratory distress leading to respiratory failure. Surgical decompression could not be performed and the patient with findings of myelopathy, respiratory distress and disseminated intravascular coagulation died at the age of 2 years.

In conclusion achondroplasia and Down syndrome are recognizable genetic syndromes with distinct genetic etiologies. The co-occurrence of these conditions in the same individual is quite rare and may be associated with increased morbidity and mortality.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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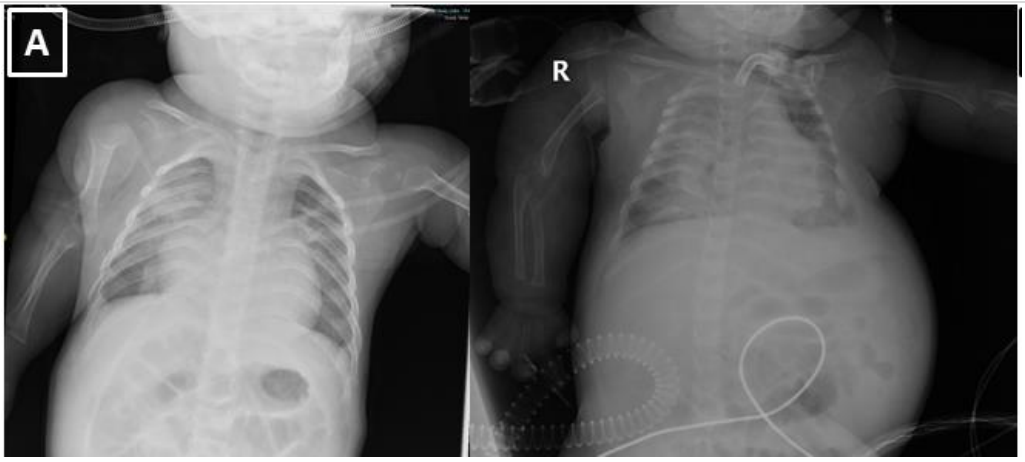
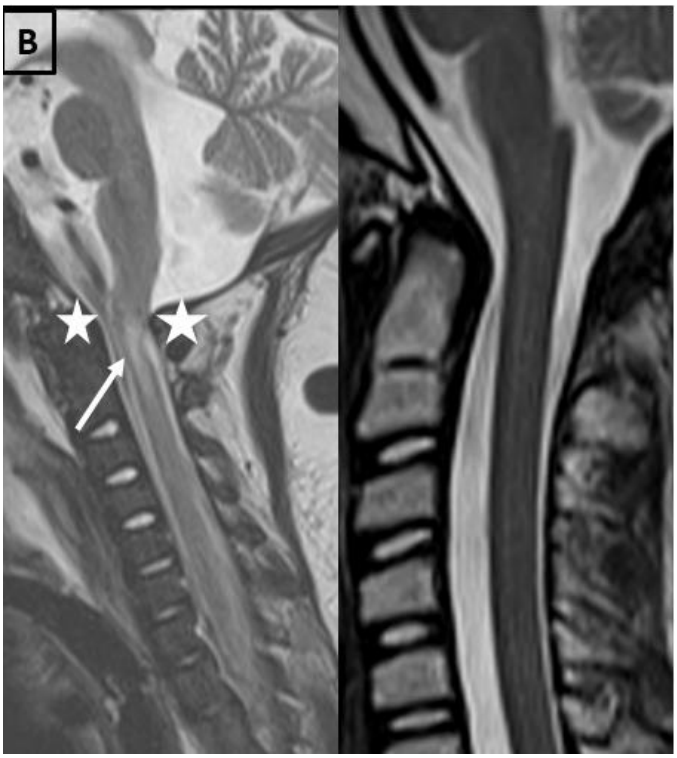
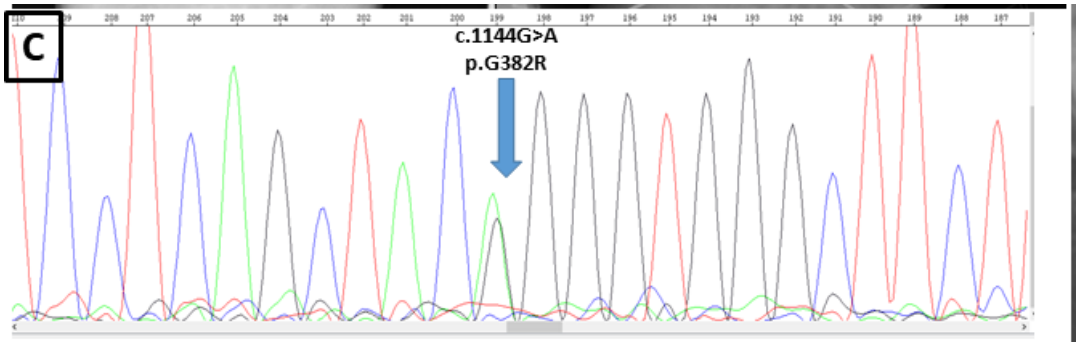


A.Radiographic evaluation of the patient revealed rhizomelic shortening of the upper extremities, metaphyseal irregularities and short long tubular bones. Please not that the interpedincular distance of the lumbar vertebrae is not widening caudally, a typical finding of achondroplasia.



B. Cranial magnetic resonance sagittal T2-weighted image demonstrates stenosis of craniocervical junction (between the stars) and spinal cord compression and myelopathy (arrow). Please compare the findings with normal craniocervical junction a sex and age-matched control



C.The Sanger sequencing revealed a *de novo* [c.1144G>A] [p.G382R] in FGFR3 gene.