Case Report

Kenny-Caffey syndrome type 1 in an Egyptian girl

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ABSTRACT

Kenny-Caffey syndrome type 1 (KCS1) (OMIM 244460) is a rare syndrome characterized by growth retardation, uniformly small slender long bones with medullary stenosis, thickened cortex of the long bones, hypocalcemia possibly with tetany at an early age and normal intelligence. The primary outcome of KCS1 is short stature. We present here an Egyptian girl aged 32 months with typical feature of KCS1.

Key words: Dysmorphic, growth retardation, hypoparathyroidism, Kenny-Caffey syndrome type 1, Sanjad Sakati Syndrome

Introduction

Kenny-Caffey syndrome type 1 (KCS1) (OMIM 244460) is a rare autosomal recessive syndrome characterized by growth retardation, dysmorphic features ,uniformly small slender long bones with thickened cortex and medullary stenosis. Hypocalcemia with hypoparathyroidism presents at an early age.[1] The true prevalence of KCS1 in Egypt is unknown. Herein, we present a 32 -month-old Egyptian girl with KCS1who had all the characteristic clinical, biochemical , radiological and molecular genetics abnormalities of the syndrome.

Case Report

A 32-month-old Egyptian girl was referred to our pediatric endocrinology unit for evaluation of poor growth. She was the second-born female child to consanguineous Egyptian parents with the other sibling being normal. She was borne at term by normal vaginal delivery in a private hospital and cried immediately at birth. Her birth weight was 1.5 kg and length was 35 cm.At the age of 12 days, she developed multifocal seizures and hypocalcemia was detected at that time. Serum parathormone (PTH) level was not checked due to lack of facilities.The seizures were controlled with intravenous calcium infusions. Later, she required calcium and alfacalcidol to maintain her calcium levels. She has been on calcium and vitamin D supplements since then. At the age of one year her weight was 4.800 kg and height was 48 cm. She was thriving poorly in spite of her good appetite.. There was no history of recurrent infection or previous hospital admission. On examination, she was found to be severely growth retarded with normal mentality, her weight was 7 kg, height 60 cm, and head circumference 38 cm (all far bellow third percentile) [Figure 1], the upper segment to lower ratio was normal, dysmorphic facies: (microcephaly, deep-set eyes, peaked nose, thin lips, micrognathia, low set ears, depressed nasal bridge) [Figure 2]. Systemic examination including the cardiovascular system was within normal limits. Ophthalmic examination did not reveal any abnormality. Investigations revealed that hemogram, liver, renal function, and urine analysis were normal. She had low total calcium 7.4 mg/dL (normal range, 8.5 mg/dL to 10.5 mg/dL), low ionized calcium 3.3 mg/dL (normal range, 4.5 mg/dL to 5.6 mg/ dL), raised serum phosphate 8.2 mg/dL (normal range, 2.4 mg/dL to 4.1 mg/dL), raised alkaline phosphatase 344 U/L (normal range, 30 U/L to 95 U/L) and low intact PTH 6.2 pg/ mL (normal range, 12 pg/mL to 72 pg/mL). Abdominal ultrasound was normal. Radiograph of long bones showed cortical thickening with

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medullary stenosis, and skull X-ray revealed absent diploic space in the skull bones [Figures 3 and 4], Computed tomographic scan of brain was normal. Cytogenetic and fluorescent *in situ* hybridization studies were normal. The diagnosis was confirmed genetically by detection of homozygous deletion of 12 bp (155-166 del) in exon 3 of the tubulin specific chaperone E gene (TBCE gene). The parents were heterozygous carriers of this mutation.

Discussion

Kenny- Caffey syndrome is a rare hereditary skeletal disorder, first reported by Kenny and Linarelli in 1966.[2] Caffey described its radiological features in 1967.[3] Lee described the classical facial features in 1983.[4] Up to our knowledge, this is the first reported case of KCS1in Egypt.

Our index case was suspected to have KCS1 in view of severe growth retardation, typical facial features, hypocalcemia, hypoparathyroidism and characteristic bone changes. The diagnosis was confirmed by molecular genetics study which revealed deletion of the TBCE gene. The gene TBCE encodes a protein that participates in beta-tubulin folding.[5] All these findings bear a resemblance to a similar syndrome classified as autosomal dominant KCS2 (OMIM 127000).[6] However, macrocephaly, corneal and retinal calcification, congenital cataracts, hypophosphataemia, cellular immune defects are important distinguishing features. Accordingly, the differentiation between the two syndromes must be based on proper evaluation of the clinical picture, biochemical, and molecular diagnosis if possible.[7] KCS1 should be also differentiated from Sanjad–Sakati syndrome (SSS; OMIM 241410) which is an autosomal recessive disorder first reported in 1988[8] and confirmed by definitive report in 1991.[9] It has been reported almost exclusively in the Middle Eastern population and is characterized by congenital hypoparathyroidism, retarded growth, mental retardation, seizures and a characteristic physiognomy.[10] Although the skeletal findings seen in KCS1 have not

Figure 1: Girl with Kenny-Caffey syndrome age 32 months showing severe growth retardation

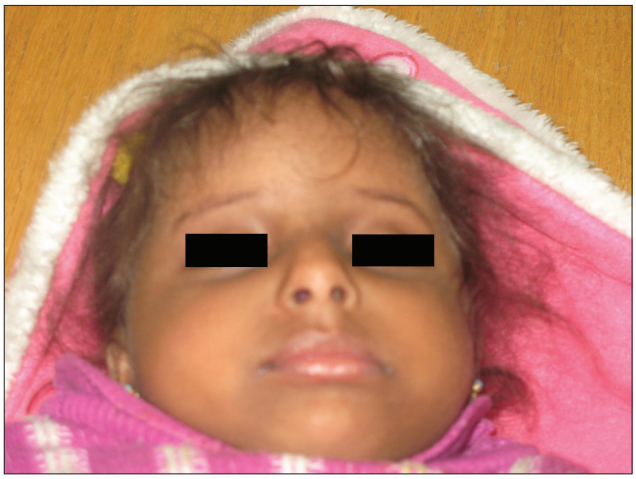

Figure 2: Girl with Kenny-Caffey syndrome showing, depressed nasal bridge, micrognathia, upslanting, deep-set eyes and low set ears

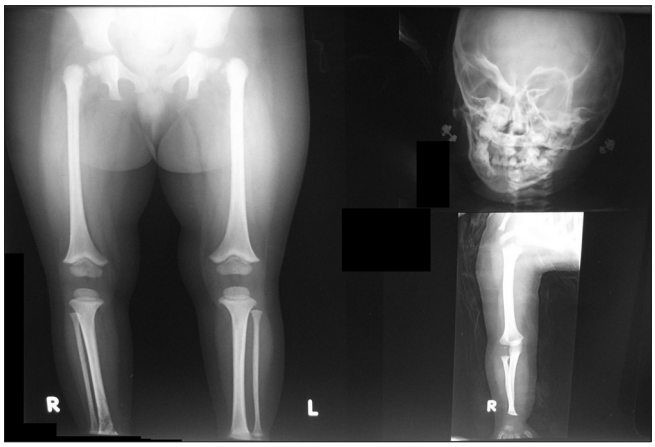

Figure 3: Radiographs of long bone showing cortical thickening with medullary stenosis

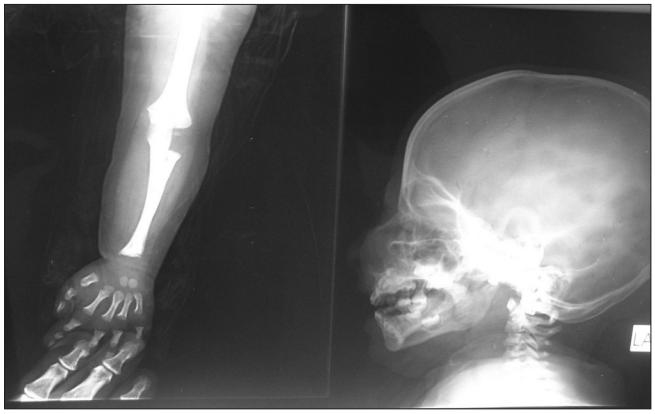

Figure 4: Skull X-ray showing absent diploic space in the skull bones

been described in SSS patients, the clinical similarities combined with the linkage of both conditions to chromosome 1q42– q43[11] suggested that the two are at least allelic disorders if not the same condition. The molecular pathology of this syndrome was shown to be due to mutations in the TBCE gene in chromosomal area 1q42– q43.[12] SSS is not uncommon in the Gulf area, especially Saudi Arabia and Kuwait: the incidence in Saudi Arabia varies from 1:40 000 to 1:100 000 live births.[13] In Kuwait, some authors consider it a variant of KCS1.[6] On the other hand, overlap with other syndromes such as CHARGE association, DiGeorge, velo-cardiofacial and CATCH 22 could be raised. The common findings are hypocalcaemia, growth retardations, hypoparathyroidism, and abnormal facial features. However, the absence of characteristic phenotype of KCS1, normal chromosomal and FISH studies and the characteristic molecular pathology will differentiate.[1]

Parvari *et al.*[1] demonstrated mutations in the TBCE gene in both autosomal recessive KCS and SSS. Accordingly, the confusion raised by some authors who refer to an autosomal recessive type of KCS has to be addressed. The similarity of the clinical picture and molecular basis of both syndromes strongly suggest the syndromes are identical/allelic. Reviewing literatures revealed that previous reports of cases of KCS1, KCS2, and SSS had been diagnosed during the neonatal period due to phenotypic picture, hypocalcaemia/seizures,or raised awareness of the syndrome among paediatricians and geneticists.[6,11,13] The delay of the diagnosis of our index may be attributed to lack of awareness of paediatrician to these syndromes in our area.

Therapeutic options for KCS1 patients are limited to palliative therapy and correction of hypocalcaemia.[1] However, prevention could be achieved through preimplantation genetic diagnosis (PGD) and carrier detection.[14] We hope that this report will stimulate the recognition of the syndrome in other families and elsewhere. In conclusion**,** early recognition of children KCS1 will lead to proper treatment of patients and prevent associated co morbidities.

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