Raine syndrome associated with cytomegalovirus infection

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Intracranial calcification, periosteal proliferation and microcephaly, which represent the clinical features of the congenital cytomegalovirus infection, can also be seen in a rare disorder named Raine syndrome. This clinical entity has been reported in eight families so far. Here, we report a new patient with clinical features of the Raine syndrome associated with cytomegalovirus infection. Although this may be a chance association only, the condition raised the question of whether early intrauterine CMV infection may contribute to the Raine phenotype.

Key words: Raine syndrome, intracranial calcification, cytomegalovirus.

Raine et al.[1] (1989) described a syndrome characterized by microcephaly, hypoplastic nose, exophthalmos, gum hyperplasia, cleft palate, triangular mouth and low-set ears. Radiographs show diffuse generalized osteosclerosis with subperiosteal thickening. Subsequently, Al Mane et al.[2] reported another case with the same pattern of anomalies with intracranial calcification as an additional sign. The condition was termed Raine syndrome by Kan and Kozlowsli[3]. So far, 12 cases in eight families have been reported. Here, we report a new patient with clinical features of the Raine syndrome associated with cytomegalovirus (CMV) infection.

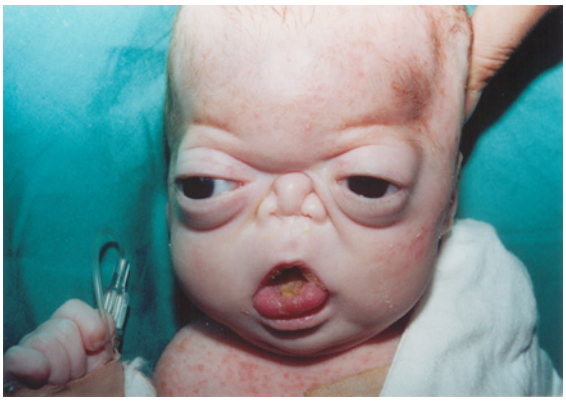

Fig. 1. Frontal view of the patient's head with proptosis, depressed nasal bridge and triangular mouth.

Case Report

A two-hour-old female newborn infant was referred to our hospital because of multiple congenital anomalies and respiratory distress. The patient was born normally to a 22-year-old gravida 2 para 2 healthy mother at the 38th week of gestation. The parents were first cousins and an older sister was in good health. There was no history of disease and no use of drugs such as warfarin or phenytoin during pregnancy. On physical examination, her weight was 2500 g (10-25th percentile), length 47 cm (25th percentile) and head circumference 31 cm (<10th percentile). Craniofacial abnormalities included a hypoplastic nose, proptosis, triangular mouth and low-set ears (Fig. 1). The anterior fontanelle was large and bulging. The hard palate was intact but narrow and high-arched. The ophthalmological examination showed normal ocular findings except for severe proptosis. Echocardiography was normal. Chromosome analysis revealed 46,XX karyotype. Cranial computerized tomography (CT) scan showed widespread focal cerebral calcifications (Fig. 2). Radiographs of the skeleton showed a generalized increase in bone density. The medullary cavities of the long bones were poorly differentiated from the cortex and irregular thickening was present along the diaphyses (Fig. 3). Lateral radiograph of the patient showed diffuse osteosclerosis (Fig. 4). Abdominal ultrasonography showed no abnormality. Laboratory findings included:

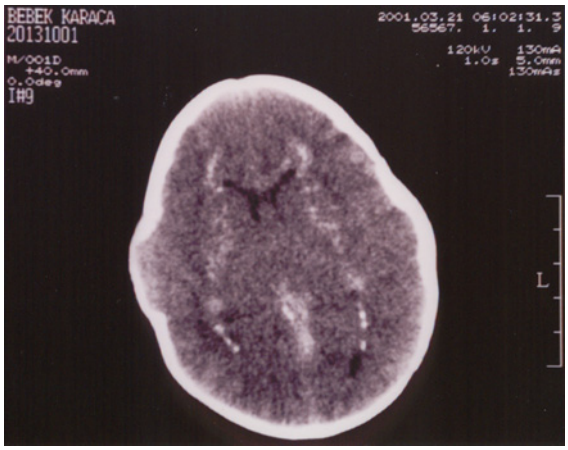

Fig. 2. Cranial computed tomographic scan demonstrated widespreada focal cerebral calcifications.

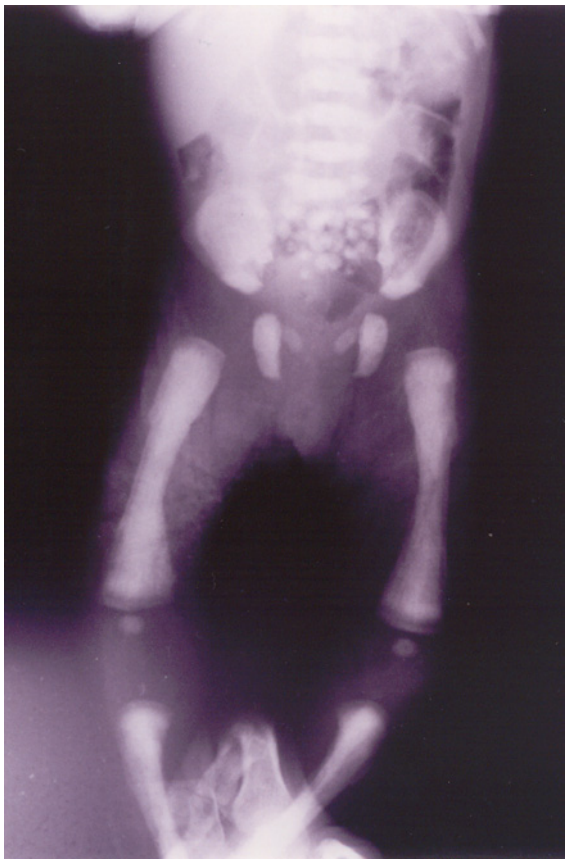

Fig. 3. The pelvis and lower extremities: osteosclerosis with impaired cortico-medullary differentiation and irregular periosteal thickening.

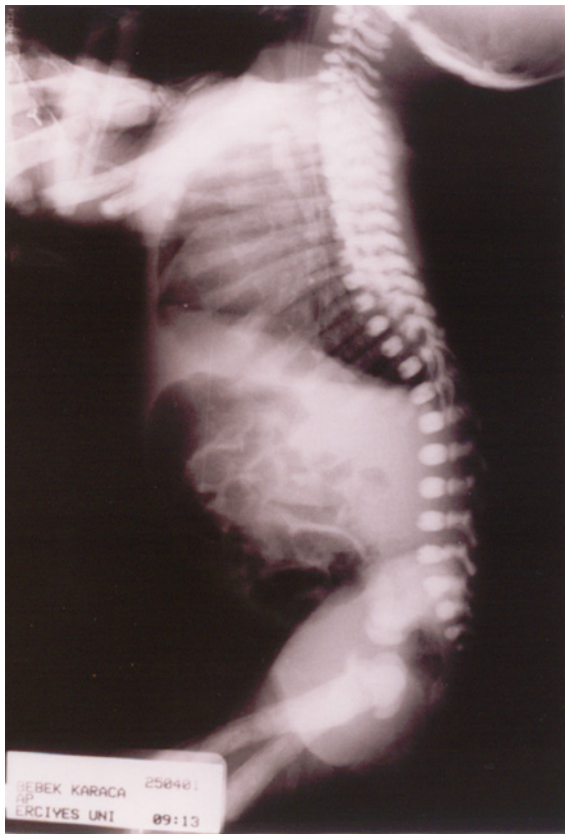

Fig. 4. Lateral radiograph of patient showed diffuse osteosclerosis.

hemoglobin 15.6 g/dl, hematocrit 48%, white blood cell count 13,000/mm^3, platelets 106,000/mm^3, serum calcium 8.4 mg/dl, phosphate 3.1 mg/dl, glucose 67 mg/dl, total protein 5.7 g/dl and albumin 3.2 g/dl. The level of alkaline phosphatase was slightly increased (813 U/L). Her total T3 was 227 ng/dl, total T4 9.59 µg/dl, TSH 1.87 mIU/ml, growth hormone 23.05 mIU/ml, and cortisone 12.70 µg/dl.

Initially, the clinical features suggested a diagnosis of congenital CMV. CMV DNA (Hybrid Capture, CMV DNA, Digene, USA) was detected in the blood. The patient was ventilated for five days and once she was stabilized, the parents requested that further active treatment be discontinued. The child was fed by orogastric route and discharged.

Discussion

We have described a patient presenting a clinical picture compatible with the diagnosis of Raine syndrome. This syndrome is characterized by generalized osteosclerosis with craniofacial anomalies and intracranial calcifications.

The etiology of Raine syndrome is still obscure. No genetic, metabolic, infective, toxic or physical cause has yet been established for this condition in the literature. Until now, only 12 cases of Raine syndrome have been reported[4]. These cases occurred in eight families, of which two had three affected siblings. Consanguinity was present in six of the eight parents. No chromosomal anomaly was reported in all described cases. Autosomal recessive inheritance seems very likely. All infants died from respiratory failure in the neonatal period[4,5].

Periosteal proliferation, microcephaly and intracranial calcification can be clinical features of intrauterine infections such as Toxoplasma and CMV[6]. However, an association between sclerosing bone dysplasia and intracranial calcification has been established in some conditions such as autosomal recessive osteopetrosis with renal tubular acidosis and carbonic anhydrase II deficiency. Recently, Sazgar et al.[7] reported two brothers with intracranial calcifications, a sclerotic bony disorder and bilateral exudative retinopathy. There are some phenotypic similarities between Raine syndrome and warfarin-induced embryopathy. Nasal hypoplasia and punctuate calcifications, especially in the axial skeleton, calcaneus and epiphyses of the long bones, are also described in warfarin-induced embryopathy[8]. Craniofacial abnormalities are also seen in fetal hydantoin syndrome[9,10]. Fetal hydantoin embryopathy is characterized by growth retardation, microcephaly, midfacial hypoplasia and cleft palate[9]. However, our patient's mother did not receive any medicine during pregnancy.

Rickert et al.[4] suggested that genetic defect with disturbance of calcium metabolism is the likely etiology of Raine syndrome. In our case, non-specific mild elevation of the alkaline phosphatase was the only feature suggestive of a metabolic disturbance.

Our patient showed all clinical features of Raine syndrome, but analysis of the blood sample from our patient, taken on the second day of age, confirmed the presence of CMV DNA, indicating a CMV infection. However, there was no other associated evidence of CMV infection such as hepatosplenomegaly, retinopathy or jaundice. Our patient's parents are first cousins and have a healthy girl. Parental consanguinity supports suggestions that this is an autosomal recessive disorder. Although this may be a chance association only, the condition raised the question of whether a congenital CMV infection may contribute to the Raine phenotype. Further reports might clarify if this is merely a coincidence.

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