17p13.3 Class I Microduplication in a Newborn with Microcephaly, Aortic Stenosis and Dysmorphic Facial Features

A Ho,[1] A Liu,[1] KS Lun,[1] T Tam,[2] K Chan,[2] E Lau,[2] M Tang,[2] T Tan,[1] B Chung[1,2]

[1]Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital; [2]Prenatal Counseling Unit and Prenatal Diagnostic Laboratory, Department of Obstetrics and Gynaecology, Tsan Yuk Hospital, The University of Hong Kong, Hong Kong

Background: Deletion of chromosome 17p13.3 is known to result in Miller-Dieker Syndrome. Microduplication of the same genomic region results in a distinctive clinical syndrome (Roos et al. 2009). We report a newborn presented with dysmorphic features, microcephaly and congenital heart disease, who was confirmed to have 17p13.3 microduplication syndrome by array comparative genomic hybridization (aCGH).

Clinical information: The proband was the 2nd child of a non-consanguineous Chinese couple. He was noted to be microcephalic from fetal USG in China. He was born full term via LSCS with normal Apgar scores. His head circumference, body weight and height at birth were 31.5 cm (<3rd percentile), 3.33 kg (25-50th percentile) and 48 cm (10th percentile) respectively. Distinct facial features including flat midface, posteriorly rotated and low-set ears, fleshy earlobes and triangular chin. Echocardiogram revealed valvar aortic stenosis and tiny patent ductus arteriosus. USG brain was normal. Karyotype and FISH for Elastin gene were normal. aCGH by NimbleGen CGX-12 array identified a 790 kb copy number gain in the 17p13.3 region involving the YWHAE gene, but not the PAFAH1B1 gene.

Bruno et al (2010) proposed that there are 2 classes of 17p13.3 microduplication. Class I involves YWHAE gene, but not PAFAH1B1 gene while Class II involves PAFAH1B1 gene, with or without CRK and YWHAE genes. Class I 17p13.3 microduplication is associated with autistic features, developmental delay and subtle dysmorphic features such as pointed chin, fleshy ears and cupid bow. Microcephaly has been reported but often there is a tendency to post-natal overgrowth. Only one patient in Bruno's cohort was noted to have cardiovascular manifestations, namely aortic root dilatation and mitral valve prolapse.

Conclusion: To our knowledge, this is the first patient with 17p13.3 microduplication syndrome reported in Chinese. Growth and neuro-development need to be closely monitored. The young age of diagnosis together with the associated tendency to autism spectrum disorder pose a challenge in genetic counseling.

Infantile Systemic Hyalinosis Presenting as Multiple Joint Pain in a Pakistani Infant Girl

BHY Chung, E Lausch, A Superti-Furga

Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong; Lausch E, Centre for Pediatrics and Adolescent Medicine, University Hospital Mathildenst, Freiburg, Germany; Superti-Furga A, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland

Background: Infantile systemic hyalinosis (ISH) is a rare autosomal recessive disorder characterized by abnormal hyaline deposits in the papillary dermis and other tissues. It presents in early infancy with severe pain with movement, progressive joint contractures, thickened skin and hyperpigmented macules over bony prominence. Gingival hypertrophy, skin nodules, perianal masses are common but late findings. We report a female infant with ISH and subsequently confirmed to have known pathogenic mutations in the ANTXR2 gene.

Clinical information: The proband was the 3rd child of a Pakistani couple who were first cousins. Her elder sister passed away at 8 months with unknown cause. She was born full term by NSD with normal growth parameters and Apgar scores. Newborn examination was normal. She presented with decreased limb movement at 3 months. Clinical assessment showed that limb movement was limited by severe pain; her ears were simple but prominent and there were hyperpigmentation over the finger knuckles and ankles. Skeletal survey showed metaphyseal/submetaphyseal widening. Bone marrow examination excluded myeloproliferative disorders. The absence of fever and skin rash, normal ophthalmologic examination and normal levels of serum inflammatory markers made the diagnosis of Chronic infantile neurolological, cutaneous and articular (CINCA) syndrome unlikely.

As limb pain and the skin findings could be the only findings in the early stage of ISH, genetic testing was offered to the parents with genetic counseling. A known pathogenic homozygous mutation, c.[652T>C] was found in the ANTXR2 gene causing an amino acid substitution in codon 218, p.C218R, confirming the diagnosis of ISH. The parents were carriers of the same mutation.

Conclusion: Although ISH is more common in ethnic groups with consanguineous marriage, it has been reported in Chinese. This patient developed protein-losing enteropathy at 5 months, perianal masses at 6 months and mild gingival hypertrophy at 8 months. The prognosis of patients with ISH was poor and they usually die at infancy with recurrent infections and malnutrition.