

Partial Deletion 9p Syndrome in Malaysian Children

H B Chew, MRCPCH, M K Thong, FHGSA (Clinical Genetics)

Genetics and Metabolism Unit, Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

SUMMARY

We report the first two Malaysian children with partial deletion 9p syndrome, a well delineated but rare clinical entity. Both patients had trigonocephaly, arching eyebrows, anteverted nares, long philtrum, abnormal ear lobules, congenital heart lesions and digital anomalies. In addition, the first patient had underdeveloped female genitalia and anterior anus. The second patient had hypocalcaemia and high arched palate and was initially diagnosed with DiGeorge syndrome. Chromosomal analysis revealed a partial deletion at the short arm of chromosome 9. Karyotyping should be performed in patients with craniostenosis and multiple abnormalities as an early syndromic diagnosis confers prognostic, counselling and management implications.

KEY WORDS:

9p deletion, Craniostenosis, Trigonocephaly, Karyotyping, Genetic counselling

INTRODUCTION

Alfi and colleagues first described "Deletion 9p syndrome" in 1973¹. In most cases, the aetiology is a breakpoint located at band 9p22². 85% are due to de novo deletions and 15% are due to parental translocation. In addition, ring chromosome 9 is reported to have similar phenotype as deletion 9p syndrome. The critical region for the 9p deletion syndrome maps to a 46Mb region in 9p22-p23. The defining features of this condition were reported as craniostenosis with trigonocephaly, upslanting palpebral fissures and hypoplastic supraorbital ridges. Other common abnormalities are mental retardation with a mean IQ of 48²; abnormal digits with long middle phalanges and short distal phalanges; cardiovascular defects commonly ventricular septal defects, patent ductus arteriosus or pulmonary stenosis and gonadal abnormalities¹⁻². Terminal deletion of 9p is associated with male to female sex reversal and primary hypogonadism. Sex ratio for this disorder is balanced and symptoms and signs are typically present from birth.

CASE REPORTS

Case 1

This 11 month-old girl was born to non-consanguineous parents at term with a birth weight of 4kg. She had unremarkable family and antenatal history. On day 2 of life, she presented with hypoglycaemia and methicillin resistant *Staphylococcus aureus* (MRSA) sepsis. At presentation, she

was noted to be dysmorphic. Craniofacial morphology included craniostenosis of the metopic suture leading to trigonocephaly, broad nasal bridge, short nose with anteverted nares, long philtrum, upslanting palpebral fissures and epicanthal folds, highly arched eyebrows, mid-facial hypoplasia and low set ears with horizontal ear creases. She also has long digits in the hands and feet with extra flexion creases in the fingers; widely spaced nipples; underdeveloped female genitalia and anterior anus (Fig. 1). Cardiovascular examination and echocardiogram showed a 2mm atrial septal defect and mild branched pulmonary artery stenosis. Karyotyping yielded the following results: 46, XX, del (9)(p22). Twenty three cells were examined and all contained this deletion resulting in monosomy for the region 9p22-9pter. Parental chromosomes were normal. Hormonal evaluation of luteinizing hormone, follicular stimulating hormone and oestradiol were consistent with pre-pubertal values. On follow up at six months of age, her growth and development were normal.

Case 2

The second child of unrelated parents, this 2 years and 5 month-old boy was delivered at full term with a birth weight of 3.4 kg. His family and antenatal histories were unremarkable. He was noted to be dysmorphic when presenting with slow feeding and vomiting in the first week of life. Physical examination revealed metopic sutures, rotated ears with pre-auricular pits and abnormal ear lobules, anteverted nostrils with long philtrum, thin upper lip, high arched palate, small mouth and jaw, long slender fingers, suprascrotal testes and hypotonia. There was a systolic murmur which was confirmed by echocardiogram to be a patent ductus arteriosus. A low calcium level of 1.65mmol/L was noted and together with his dysmorphism, a clinical diagnosis of DiGeorge syndrome was proposed. Three-dimensional cranial computerised tomogram showed metopic sutures with some parts of the coronal suture fused with normal underlying brain parenchyma. The hypocalcaemia subsequently resolved spontaneously. Thirty cells were analysed in karyotyping and revealed 46, XY, del (9)(p22) in all cells. Parental chromosomes were normal. On follow up assessment at seven months of age, he exhibited mild hypotonia with craniostenosis and trigonocephaly, arched eyebrows with synophrys, narrow palpebral fissures, small low-set dysplastic ears and small mouth. At two years old, the above facial features and generalised hypotonia persisted. Synophrys was prominent (Fig. 2). He was estimated to have moderate global developmental delay. At the time of reporting, he was too young for formal IQ testing.

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Corresponding Author: Chew Hui Bin, Genetics and Metabolism Unit, Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia Email: hbchew155@hotmail.com

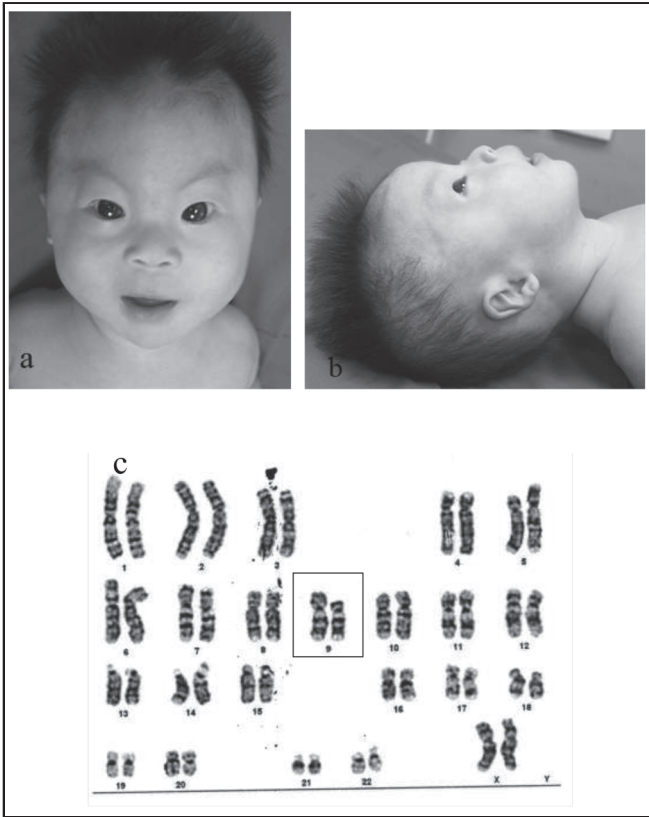


Fig. 1: Partial deletion 9p Syndrome, A and B: Note the prominent forehead with metopic ridge, trigonocephaly, upslanting palpebral fissures, epicanthal folds, highly arched eyebrows, mid-facial hypoplasia with short nose and anteverted nares, low set ears with horizontal ear crease. C: Chromosome spread showing partial deletion for the region 9p22-9pter

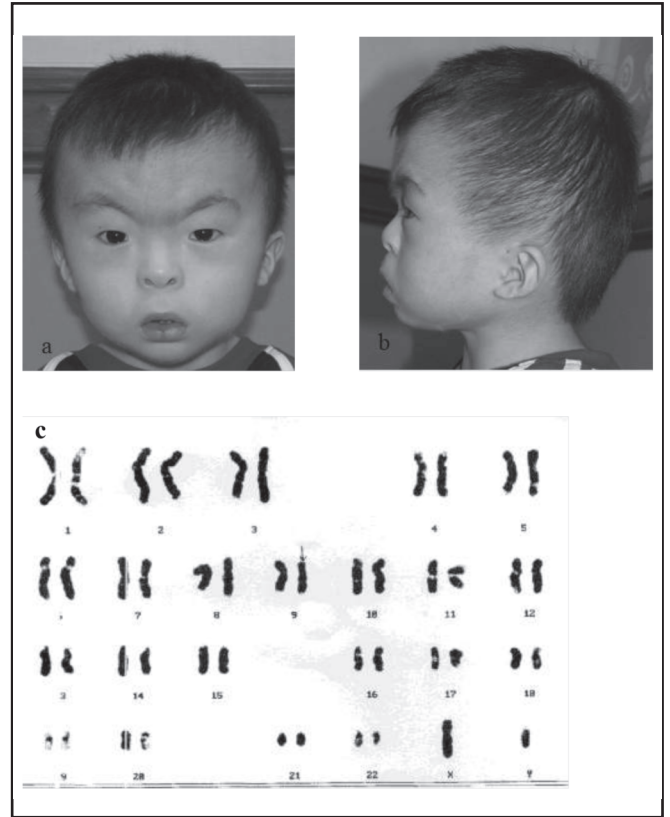


Fig. 2: Partial deletion 9p syndrome at 2 years of life, A and B: Note persistent narrow palpebral fissures, broad nasal bridge, rotated dysplastic ears with pre-auricular pits, anteverted nostrils with long philtrum, trigonocephaly, microstomia and arched eyebrows and synophrys. C: chromosome spread showing partial deletion 9p22

DISCUSSION AND CONCLUSION

Partial deletion 9p syndrome is a well-described but rare clinical entity. This is the first report of this syndrome in Malaysian children. Diagnosis can be challenging as the normally flat facial profile of Southeast Asian children may mask the dysmorphic features such as hypoplastic supra-orbital ridge. A clinical diagnosis of DiGeorge Syndrome was made in one of our patient because of the presence of hypocalcaemia. In many developing countries, cytogenetic services may not be easily available. These cases highlight the importance of performing karyotyping in children who appear syndromic.

The dysmorphism of partial deletion 9p syndrome is typical regardless of the length of deleted segment. The exception occurs when it is associated with other unbalanced chromosomal rearrangements e.g. partial trisomies. These are inherited from a balanced translocation carrier². Furthermore, up to 15% of partial deletion 9p syndrome may be due to balanced chromosomal rearrangement in a parent. Therefore performing a chromosomal study in these infants is important to aid counselling of recurrence risk.

The diagnosis of partial deletion 9p syndrome has implications for counselling and management. Closure is possible with a definitive diagnosis and prognosis can be predicted. Whilst normal growth and development was seen in one of our patient at six months of age, global developmental delay is the rule. Therefore support with learning through early intervention programs should be instituted when the diagnosis is made. Maintaining early intervention and regular follow up can be difficult. Parental education needs to be emphasised because disabled children with a genetic cause are often misconstrued in this society to require no treatment or follow up. Monosomy of the distal 9p has been reported to be associated with a wide range of gonadal dysgenesis including sex reversal, hypo/agonadism, streak gonads, cryptorchidism and hypoplastic testes. Our first patient had underdeveloped female genitalia and the second patient had cryptorchidism. Although sex hormones were normal at the time of reporting, re-evaluation is essential. Since gonadal dysgenesis predisposes to gonadoblastoma³, parents have to understand the importance of regular surveillance. Some of the less well described associations of deletion at the 9p region include acute lymphoblastic leukaemia⁴ and autistic spectrum disorder⁵.

Chromosome 9p has also been implicated in linkage studies of bipolar affective disorder. These are important burdens of disease that should be anticipated. Surgical corrections of congenital cardiac defects, trigonocephaly, cleft palate and ambiguous genitalia may also form part of the management plan.

Life expectancy is normal except in cases where there is gross visceral malformation. This is rare unless there are associated unbalanced chromosomes. Transient hypocalcaemia as found in one of our patients has not been reported in this condition. More studies are needed to elucidate whether this is a definite association.

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