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A case of partial trisomy 13 presenting with hyperinsulinaemic hypoglycaemia

第13對染色體局部三倍體病及胰島素過高引致的血糖過低

We report on a newborn baby with partial trisomy 13 who presented with multiple dysmorphic features and hyperinsulinaemic hypoglycaemia. Cytogenetic study on peripheral blood lymphocytes showed 47,XY,+mar in all cells analysed; fluorescent in situ hybridisation showed that the marker was solely derived from chromosome 13. The final karyotype was 47,XY,+del(13)(q14q32). Milk formula through a nasogastric drip and intravenous glucose infusion were given to prevent further hypoglycaemia. However, the baby developed occasional episodes of hypoglycaemia during bolus feeding. Hence, diazoxide was given, at a dosage of 10 mg·kg⁻¹·d⁻¹ from day 24. Thereafter, no hypoglycaemic episodes were detected. Subsequent follow-up revealed satisfactory growth, global developmental delay, and left divergent squint.

本文報告的病例，為一位患有第13對染色體局部三倍體病的初生嬰兒，特徵是嬰兒出現多個畸型的特點以及由胰島素過高引致的血糖過低。利用細胞遺傳學技術來分析外周血淋巴細胞，結果顯示所有接受分析的細胞均為47,XY,+mar。熒光原位雜交技術發現標記純粹衍生自第13對染色體。最終的核型為47,XY,+del(13)(q14q32)。我們用鼻胃輸注器來給病嬰連續地餵養特別配製的嬰兒奶，並進行葡萄糖靜脈輸液，以防止血糖水平進一步下降。當嬰兒轉到間斷式餵養期間，曾間歇出現血糖過低，所以從第24天開始施以二氮嗪，劑量為每天10 mg/kg，施藥後便再沒有發現這種情況。隨後的跟進顯示，嬰兒的成長令人滿意，整體發展延後，並有左向的外斜視。

Introduction

Partial trisomy 13 is a rare chromosomal abnormality. Affected patients survive longer than those with complete trisomy 13, although the correlation between phenotype and karyotype is often complicated by the co-existence of abnormalities involving other chromosomes. Rogers¹ and Tharapel et al² reviewed 35 and 62 cases, respectively, and found that the features of patients with proximal 13q trisomy were different from those with distal 13q trisomy. Persistence of foetal haemoglobin and increased nuclear projections of polymorphonuclear leukocytes are consistently associated with proximal 13q trisomy. Rogers¹ commented that these features are actually diagnostic of 13q12 and 13q14 trisomy. Other features such as a depressed nasal bridge, cleft lip or palate, and clinodactyly are also more commonly found in individuals with proximal 13q trisomy. In individuals with distal 13q trisomy, common features include haemangioma, bushy eyebrows, long curled eyelashes, a prominent nasal bridge, a long philtrum, a thin upper lip, a highly arched palate, and hexadactyly.

Hyperinsulinaemic hypoglycaemia is a genetically heterogeneous condition. Multiple disease loci have been mapped, and associated mutations have been identified in several genes, which include those encoding the sulphonylurea receptor (the *SURI* gene), potassium channel (*KCNJ11*), glucokinase (*GCK*), and glutamate dehydrogenase 1 (*GLUD1*). The disease can be inherited in both autosomal dominant and autosomal recessive manners. However, there have been no cases of hyperinsulinaemic hypoglycaemia associated with partial trisomy 13 in the literature. To the best of our knowledge, there is only one case report of

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hyperinsulinaemic hypoglycaemia in an infant with mosaic trisomy 13.³ We report on a patient with pure partial trisomy 13 involving both the proximal and distal segments of the chromosome, who presented with the unusual feature of hyperinsulinaemic hypoglycaemia and dysmorphic features.

Case report

The patient was a Chinese preterm baby boy born at the Princess Margaret Hospital in January 2000 after a gestation of 35 weeks and 5 days with birthweight of 2380 g, which was appropriate for his gestational age. The parents were non-consanguineous; this was their first child, and they had no history of abortion. The pregnancy had been complicated, however, by positive urine culture of group B streptococcal bacteria. Furthermore, antenatal ultrasonography had shown a dilated renal pelvis and short femur in the foetus. Thus, amniocentesis was performed and showed 47,XY,+mar. The parents' karyotypes were normal.

The baby developed hypoglycaemia on the first day of life, presenting with cyanosis and apnoea, and he required intravenous dextrose infusion. The lowest detectable blood glucose level was 0.6 mmol/L. Physical examination showed the following dysmorphic features: coarse facial features, low-set ears with overfolded helix, depressed nasal bridge, broad stubby nose, short columella, long philtrum, micrognathia, umbilical hernia, bilateral transverse palmar creases, right foot post-axial polydactyly, valgus deformity of the forefeet, and bilateral undescended testes. He also had mesocardia with normal cardiac structure and situs solitus. He had no hepatosplenomegaly, but an ultrasound examination of the kidneys showed bilateral hydronephrosis.

Results from complete blood tests, renal function test, liver function test, and blood gas analysis were normal. Blood culture showed negative growth. However, the baby had persistent hypoglycaemia despite repeated bolus intravenous injection of 10% dextrose solution and continuous intravenous dextrose infusion, at a rate of as high as 13 mg·kg⁻¹·min⁻¹ to maintain normoglycaemia. The insulin level was inappropriately high, at 20 mIU/L (reference range, 3-20 mIU/L), when the blood glucose level was only 2.6 mmol/L. Other investigations, including serum lactate, pyruvate, ammonia, cortisol, and growth hormone, all yielded normal results. Urine analysis for metabolic screening was normal. Ultrasonography and computed tomography of the pancreas showed no focal lesion. Eventually, a diagnosis of hyperinsulinaemic hypoglycaemia was made.

Cytogenetic study on peripheral blood lymphocytes confirmed 47,XY,+mar in all cells analysed. Chromosome painting using fluorescent in situ hybridisation showed that the marker was solely derived from chromosome 13. Karyotyping revealed that the marker chromosome was an abnormal chromosome 13 with an interstitial deletion at breakpoints of q14 and q32 (Fig). Hence, the final karyotype was 47,XY,+del(13)(q14q32).



Fig. Chromosome 13 of the patient

The three chromosomes 13 of the patient in metaphase, prepared by Giemsa banding (GTG banding) technique, are placed on the left side of the ideogram. The extra and shortened chromosome 13 has an interstitial deletion at breakpoints of q14 and q32

Oral feeding was started on day 2. Bolus feeding was changed to a continuous milk infusion through nasogastric tube on day 6 because of an unstable blood glucose level with occasional hypoglycaemia. The energy content of the milk was also increased gradually to prevent further hypoglycaemia. The maximum concentration of 28 calories per ounce (170 calorie/kg/day) was established on day 12. Intravenous glucose infusion was gradually tapered off over 2 weeks. Between day 14 and day 24 of life, the feeding regimen was gradually changed back to 2-hourly and then 3-hourly. However, the baby developed occasional episodes of hypoglycaemia during bolus feeding. Hence, a course of diazoxide was started, at a dosage of 10 mg·kg⁻¹·d⁻¹ from day 24. Thereafter, no hypoglycaemic episodes were detected.

Subsequent follow-up revealed satisfactory growth, global developmental delay, and left divergent squint. The blood glucose level was stable on regular checking. Diazoxide treatment was gradually tapered off at the age of approximately 1.5 years, when feeding with milk formula with normal caloric content was started. He had no recurrence of hypoglycaemia. Blood taken at the age of 1.5 years showed persistence of foetal haemoglobin and increased polymorphonuclear leukocyte nuclear projections.

Discussion

This patient is the first case report of partial trisomy 13 with hyperinsulinaemic hypoglycaemia. The case provides a good opportunity to study the phenotype-karyotype correlation of partial trisomy 13. As expected, the patient had features characteristic of both proximal and distal 13q trisomies (Table).

Rogers¹ suggested that triplication of band 13q31 is necessary for the clinical manifestation of polydactyly. However, the patient in this case did not have 13q31 triplication but developed polydactyly, thus suggesting that this feature actually requires the triplication of the segment

Table. Patient characteristics²

| Proximal 13q trisomy | Distal 13q trisomy | Characteristics common to both trisomies |
|---|--|--|
| Strabismus | Long eyelashes | Psychomotor retardation |
| Depressed nasal bridge | Long philtrum | Low-set ears |
| Stubby nose | Umbilical hernia | Micrognathia |
| Increased polymorphonuclear leukocyte projections | Urinary tract abnormality (hydronephrosis) | Undescended testes |
| Persistence of foetal haemoglobin | Hexadactyly | |
| | Single palmar crease | |

13q32→qter. On the other hand, although haemangioma is common among individuals with partial trisomy 13 with triplicated 13q32→qter, the patient in this case did not have haemangioma.

In a case report of hyperinsulinaemic hypoglycaemia in an infant with mosaic trisomy 13,³ the patient developed hyperinsulinaemic hypoglycaemia on day 1 and depended on intravenous glucose treatment until the age of 19 days. The authors of that report speculated that the hypoglycaemia was due to a delayed maturation of the endocrine portion of the pancreas. However, we are aware that there are two genes mapped to 13q12 that modulate insulin gene expression—namely the caudal-type homeobox transcription factor 2 (*CDX2*) and the insulin promoter factor 1 (*IPF1*). The *CDX2* gene encodes a homeodomain protein that stimulates insulin gene transcription by binding to an AT-rich sequence in the insulin promoter. German et al⁴ mapped the gene to 13q12.3 by fluorescence in situ hybridisation. Mouse foetuses carrying a homozygous null *CDX2* mutation died between 3.5 and 5.5 days postcoitum, while heterozygotes manifested tail abnormalities, stunted growth, skeletal abnormalities, and multiple intestinal adenomatous polyps.⁵

The *IPF1* gene also encodes a homeodomain protein transcription factor that binds to an AT-rich element in the insulin promoter.⁶ Stoffel et al⁷ mapped it to 13q12.1 by fluorescence in situ hybridisation. The gene product may serve as a master control switch for both the exocrine and endocrine pancreatic developmental programmes. This theory was supported by expression studies in mouse embryos, which showed that the gene was initially expressed in both exocrine and endocrine cells of the pancreas, but as pancreatic development continued, expression became restricted to beta and delta cells of the islets. Gene disruption studies showed that targeted deletion of the gene leads to a 'null pancreas' phenotype.⁸ The important role of *IPF1* was confirmed in humans by reports of *IPF1* mutations identified in patients with type 2 diabetes mellitus. Stoffers et al⁹ demonstrated that homozygosity of the *FS123TER* mutation

led to pancreatic agenesis, whereas heterozygosity was associated with type 2 diabetes mellitus of early onset.

Both the patient in this case and the previously reported patient with mosaic trisomy 13 possess a triplicated segment of 13q12, which is where both the *CDX2* and *IPF1* genes are mapped. We postulate that trisomy of 13q12, by means of a gene dosage effect, increases the insulin production and secretion from the pancreatic islets. This is the most plausible explanation for the hyperinsulinaemic hypoglycaemia of the two patients. We suggest that the manifestation of hyperinsulinaemic hypoglycaemia in patients with trisomy 13 may be more common than was previously thought. The apparent lack of documentation of this manifestation may be because of the general non-specific metabolic derangement in such patients. Additionally, their usually short survival may not allow this manifestation to be detected.

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