Case of 9p deletion with multiple pathologies

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Abstract

Introduction
We report an interesting case of a partial 9p monosomy with 46XY gonadal dysgenesis, West syndrome, hypothyroidism, insulin dependent diabetes mellitus, exocrine pancreatic insufficiency, and hypertriglyceridaemia. Though cases of 9p deletion have previously been described, this is the first case of its kind reported with multiple pathologies. In this case report, we present this interesting case and the interlinking relationships between multiple pathologies.

Case Report
The child initially presented with developmental delay, microcephaly, and failure to thrive. Chromosomal analysis revealed a 46XY karyotype with deletion of the terminal portion of 9p (p2305). There was associated dysgenesis of the testes. Normal female external genitalia were found, therefore she has been raised as a female. She later went on to develop chronic abdominal pain, thought to be caused by chronic pancreatitis, which has lead to exocrine pancreatic insufficiency and insulin dependant diabetes. The finding of hypertriglyceridaemia is a possible contributory factor.

Conclusion
The relationship between oestrogen therapy, recurrent pancreatitis, hypertriglyceridaemia, and diabetes would be a very difficult one to tease out. It is possible that the genes for complex metabolic and endocrine problems are located in chromosome 9.

Introduction
We report an interesting case of a partial 9p monosomy with 46XY gonadal dysgenesis, West syndrome, hypothyroidism, insulin dependent diabetes mellitus, exocrine pancreatic insufficiency, and hypertriglyceridaemia. Though cases of 9p deletion have previously been described, this is the first case of its kind reported with multiple pathologies.

Case Report
The child is a female infant, born at 34 weeks gestation to non-consanguineous parents. She had a trouble free neonatal period but has always failed to gain weight and reach her developmental milestones. She was noted to have microcephaly.

Various neurometabolic investigations were normal, but the chromosomal analysis revealed a 46XY karyotype with deletion of 9p (p2305). Approximately half band p23 and all the material distal to it were missing. Chromosomal analysis of parents was normal suggesting that it was de novo. Phenotypically, she had normal female external genitalia pattern with normal hymen and urethral opening. Further investigations showed a normal vagina and an infantile uterus. She had no ovaries and there was evidence of streak gonads for which she underwent gonadectomy.

She presented at nine months of age with infantile spasms. EEG showed hypersynchrony, and she responded well to a course of ACTH. Following this, she was seizure free for four years, until she presented again at the age of five with two isolated episodes of generalised seizures. She went on to develop frequent vacant spells at ten years of age; EEG was suggestive of absences in the context of symptomatic generalised epilepsy, which were well controlled on sodium valproate.

At nine years of age, she developed coarse pubic hair and mild clitoral hypertrophy without other signs of puberty. The 24-hour urinary steroid profile was normal and she was thought to have had premature adrenarche. She was commenced on cyclical oestrone therapy to induce puberty at 12 years of age. She also underwent surgery for labial adhesions.

At 12 years of age, she attended A&E, with blank episodes and unresponsiveness. The routine investigations at that time showed hyperglycaemia and glycosuria with no ketonuria or acidosis. Fasting blood glucose was raised at 11.8 mmol/l. She was diagnosed with insulin dependent diabetes mellitus. Interestingly, her insulin requirements have always been low; currently 0.7 u/kg/day. HbA1c concentration has always been within normal limits. She never had diabetic ketoacidosis and her autoantibody screen was negative. This was felt to be slightly unusual in presentation and disease progression. During her annual screening for diabetes at 12 years of age, she was found to have hypothyroidism. Thyroxine supplements were commenced after persistent biochemical abnormality was noted.

She was admitted to a tertiary adolescent endocrinology unit at 15 years of age for severe recurrent abdominal pain and extreme weight loss of 7 kg in 18 months. The abdominal pain was central, varying in severity, making her double up, and sometimes lasting for a few days. These episodes were associated with steatorrhoea. She had complained of abdominal

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pain intermittently from five years of age. Investigations showed undetectable faecal elastase levels indicating exocrine pancreatic insufficiency. The urine pancreolauryl test showed low T: K quotient confirming the same. The serum amylase was very high at 1001U/l (Normal 28–100 U/l) and triglyceride level was high at 5 mmol/l (Normal 0.4–2.3 mmol/l).

At that time, she was also seen at a tertiary gastroenterology unit for the same complaints and the investigations showed normal upper GI endoscopy and abdominal biopsy. The flexible sigmoidoscopy showed focal patchy cryptitis. It was felt the abdominal pain was due to chronic pancreatitis, as no previous triglyceride levels had been performed, it was difficult to ascertain which problem had come first, the hypertriglyceridaemia or the pancreatitis, and whether the chronic pancreatitis had led to her insulin dependent diabetes.

Currently, she continues to have upper and mid-abdominal pain though her weight has improved significantly after starting Creon supplements. Her menstrual cycle is regular on oestrogen and she has been changed over to a combined preparation in view of hypertriglyceridaemia. Her thyroid function tests and triglyceride levels are now within normal limits. Her seizures are under control with sodium valproate.

**Discussion**

The chromosome 9p deletion syndrome is a fairly well-established and recognised deletion syndrome after first being described by Alfi et al. in 1973. Since then about 100 cases have been published in the literature.

A majority of these patients appear to have similar cytogenetic breakpoints in 9p22 suggesting a chromosome breakage hotspot. The deletion is de novo in half of cases. Interestingly, dysmorphic features, even when carefully analysed, do not seem to differ with the breakpoint or length of the deleted segment, as has been described in some other deleted or trisomic segments.

The diagnosis can be made at birth on clinical grounds. The clinical features of the 9p deletion syndrome include the following dysmorphic facial features: trigonocephaly, midface hypoplasia, upward slanting palpebral fissures, and a long philtrum. After infancy, it is accompanied with developmental delay and sometimes with pyramidal tract signs, epilepsy, strabismus, nystagmus, and dental anomalies.

Deletions of distal chromosome 9p24 are often associated with 46,XY gonadal dysgenesis and depending upon the extent of the deletion, the monosomy 9p syndrome. In approximately 70% of individuals with a 46 XY male karyotype, there are various degrees of sex reversal ranging from a 46 XY female with complete gonadal dysgenesis to males with mild hypospadias.

It has been previously noted that some cases of 46XY gonadal dysgenesis carry a 9p deletion and exhibit behavioural problems consistent with autistic spectrum disorder. These data suggest that a gene responsible for autistic spectrum disorder is located within 9p24. It remains to be determined if the gonadal dysgenesis and autistic spectrum disorder are caused by a single gene or if they are caused by distinct entities at 9p24.

However, normal external genitalia and normal pubertal development have been described in 46XX females with deletions of 9p suggesting that the sex determining genes on 9p play a role only in the formation of the testis or that they play a role in gonadogenesis in both sexes but that testis formation is more sensitive to changes in gene dosage. Another possibility is that the deletion has unmasked a recessive allele on the opposite chromosome 9. This mechanism has been used to explain the development of non-ketotic hyperglycinemia in a patient with 9p deletion and the method described by Hoo et al. to explain sex reversal in reported cases. Whatever the case, the factors controlling early development of the male testes are unknown.

There are likely to be many genes involved and one of them seems likely to be situated on the end of the short arm of chromosome 9 being located in 9p24. Most patients currently diagnosed with chronic pancreatitis have pain, malabsorption, and with advancing disease, diabetes mellitus. Controversy exists as to the relationship between hypertriglyceridaemia and chronic pancreatitis. Although hypertriglyceridaemia (> 500 mg/dl) is associated with recurrent acute pancreatitis, the relationship between hypertriglyceridaemia or other hyperlipidaemias and chronic pancreatitis remains to be proven.

**Conclusion**

The relationship between oestrogen therapy, recurrent pancreatitis, hypertriglyceridaemia, and diabetes would be a very difficult one to tease out. It is possible that the genes for complex metabolic and endocrine problems are located in chromosome 9. For now, we are left to speculate until more advanced techniques and knowledge in the fascinating area emerge.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**References**

3. Vinci G, Chantot-Bastaraud S, El Houate B, Lortat-Jacob S, Brauner R, Heatley V, Thibaudeau S. Association between deletion 9p and pertriglyceridaemia in a patient with 9p deletion and the method described by Hoo et al. to explain sex reversal in reported cases. Whatever the case, the factors controlling early development of the male testes are unknown. There are likely to be many genes involved and one of them seems likely to be situated on the end of the short arm of chromosome 9 being located in 9p24. Most patients currently diagnosed with chronic pancreatitis have pain, maladsorption, and with advancing disease, diabetes mellitus. Controversy exists as to the relationship between hypertriglyceridaemia and chronic pancreatitis. Although hypertriglyceridaemia (> 500 mg/dl) is associated with recurrent acute pancreatitis, the relationship between hypertriglyceridaemia or other hyperlipidaemias and chronic pancreatitis remains to be proven.

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Case report


