

The chromosome 9p syndrome with microginitalia

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ABSTRACT

We report an 18 year old male with monosomy 9p syndrome. Clinical features included microgenitalia, mental retardation with microcephaly and dysmorphic features consistent with those of the known 9p syndrome. Endocrinological investigations indicated gonadal failure with raised FSH and LH concentrations and a low testosterone level. On examination the SRY gene was found to be normal hence we support previous reports which suggest that there is a gene on 9p involved in early testes development. Furthermore agenesis of the corpus callosum is reported for the first time in 9p syndrome,

INTRODUCTION

Monosomy 9p syndrome is a well delineated chromosomal syndrome with cardinal features including psychomotor retardation, trigonocephaly, flat nasal bridge, long philtrum, and a short, broad and webbed neck. Due to a high prevalence of impaired sexual development in genetic males with 9p syndrome a gene for testis formation has been suggested to be on the distal part of 9p:9p24 (Hoo et al.1989). In this paper we present an adult male with 9p syndrome including microgenitalia. Findings from cytogenetic, molecular and endocrinological studies are presented and we review the literature on the

involvement of 9p in testis development.

CASE REPORT

An 18- year -old male is the third child of healthy and unrelated parents. The mother and father were 28 and 31 years old respectively at birth. The proband has twin elder sisters both of whom are healthy. The third pregnancy was terminated by elective abortion.The proband was born at 42 weeks after an uneventful pregnancy. Birth weight was 4000g , length was 53cm and head circumference was 37cm. Early developmental milestones were slightly delayed : Head control was achieved at 6 months, sitting at 8 months, and first step taken at 1 year and 3 months. Medical history reports undescended testes which resolved spontaneously . The proband attended a remedial class in both elementary and junior high school. For high school he transferred to a special school. On evaluation at 18 years old he scored 30 on the

Tanaka Binet Intelligence test, this is the Japanese version of the Binet test. On examination at age 18 he presented with a head circumference of 56cm. Morphological anomalies included webbed neck, flat occiput, broad nasal bridge, anteverted nostrils, narrow palpebral fissures, hypertelorism and epicanthic folds. His mouth was small with a protruding lower lip, thin upper lip and a high arched palate. His ears were low set ears with abnormal lobules. Other dysmorphic features included long philtrum, micrognathia and retrognathia (Fig 1,2)*. He had a thoracic kyphosis and a long middle phalanx. Microgenitalia was characterized by a small penis (4cm stretched), small testis and sparse pubic hair. Neurological findings included hypotonia, intention tremor, dysarthria, and exaggerated deep tendon reflexes particularly on the left side. CT scan revealed agenesis of the corpus callosum .

* Fig 1 & 2 are available on request of a reprint.

ENDOCRINE INVESTIGATIONS

Endocrine investigations were consistent with gonadal failure with a raised FSH of 40 mIU/ml (normal range 2.9-8.2mIU/ml) and an LH of 14mIU/ml (normal range 1.8-5.2 mIU/ml). After LHRH stimulation a normal response in the LH value was observed, the LH value rose to 79mIU/ml. base value. Similarly following FSHRH stimulation a normal response in the FSH value, the FSH value rose to 84mIU/ml. The concentration of testosterone was 307ng/dl (normal range 250- 1100 ng/dl).

CYTOGENETIC AND MOLECULAR ANALYSIS

Chromosome analysis, performed on 20 cultured lymphocytes with high resolution banding, showed an abnormal chromosome 9 with a terminal deletion of the short arm, 46,XY,del(9)(p22.3). FISH method confirmed the absence of a translocation with the following result obtained; 46, XY,del (9)(p22.3).ish del (9)(wcp9+). The parental chromosomes were normal. The SRY gene was amplified by the polymerase chain reaction, cloned and sequenced and no mutation found (Sinclair et al. 1990, Koopman et al. 1991, Reijo et al. 1995).

DISCUSSION

The case presented with micropenis and underdeveloped testis in addition to dysmorphic features consistent with 9p syndrome. Endocrinological analysis indicated gonadal failure as opposed to a hypothalamic hypophyseal disorder. Thus it can be inferred that the hypoplastic testis was incapable of producing sufficient androgen resulting in microgenitalia. This case is similar to three previously reported genetic male patients with 9p and impaired male sexual development. Monaghan et al (1981) described a 20 month old boy with small penis, partly descended testis, and underdeveloped scrotum. Results of endocrinological analysis were also consistent with a primary gonadal disorder. Kadotani et al (1984) reported an 8 year old boy with cryptorchism, small penis, hypoplastic scrotum and hypospadias. Finally, Szymansky et al. (1984) reported a 10 month old boy with a small penis. Hoo et al.(1989) suggest that a recessive gene on the 9p24 locus is important in the early development of testis, all of the above 4 cases presented with monosomy of 9p24 . Considerable variability has been reported regarding impairment of male sex development in cases of 9p. Abnormal genitalia ranging from complete sexual reversal (Bennett et al. 1993) to ambiguous genitalia (Ogata et al. 1997), or to microgenitalia (Monaghan et al. 1981) have been reported in approximately 70% of 46 XY 9p deletion patients. This variability may be related to the time of influence of the defective gene relative to the critical period in testis development. It has been suggested that defective androgen production during the critical period usually results in female external genitalia or ambiguous genitalia while defective androgen production post critical period usually leads to male external genitalia with microgenitalia (Ogata et al.1997). While an increasing number of reports of 9p syndrome and impaired male sexual development provide more support for a role for 9p in early testis development the mechanisms to explain the sexual

impairment remain unclear. From the genetic point of view haploinsufficiency has been suggested as one possible mode of action (Veitia et al. 1997). Haploinsufficiency syndromes tend to show a wide variety of phenotypes between individuals. Furthermore it is thought that developmental pathways are particularly susceptible to haploinsufficiency (Fisher & Scambler 1994). However it is unlikely that haploinsufficiency alone can explain the wide range of expressivity seen in relation to sexual development in 9p cases and it may be that both genetic and nongenetic factors are responsible for this phenomenon. Two other possible mechanisms cited are prezygotic mutation of the testis forming gene on the normal 9p and postzygotic somatic mutation of the normal 9p gene in developing testicular cells (Ogata et al 1997). Finally the authors wish to highlight the previously unreported finding of agenesis of the corpus callosum. The only other relationship that could be found between abnormality of the corpus callosum and 9p was that of atrophy of the corpus callosum in a case of 9p trisomy (Stern 1996).

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