Why is the retention of gonadotrophin secretion common in children with panhypopituitarism due to septo-optic dysplasia?

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Abstract

Septo-optic dysplasia (De Morsier syndrome) is a developmental anomaly of mid-line brain structures and includes optic nerve hypoplasia, absence of the septum pellucidum and hypothalamo–pituitary abnormalities. We describe seven patients (four female, three male) who had at least two out of the three features necessary for the diagnosis of septo-optic dysplasia. Four patients had hypopituitarism and yet normal gonadotrophin secretion: one of these also had anti-diuretic hormone insufficiency; three had isolated GH deficiency and yet had premature puberty, with the onset of puberty at least a year earlier than would have been expected for their bone age. In any progressive and evolving anterior pituitary lesion it is extremely unusual to lose corticotrophin-releasing hormone/ACTH and TRH/TSH secretion and yet to retain gonadotrophin secretion.

GnRH neurons develop in the nasal mucosa and migrate to the hypothalamus in early fetal life. We hypothesise that the arrival of GnRH neurons in the hypothalamus after the development of a midline hypothalamic defect may explain these phenomena.

Progress in spontaneous/premature puberty in children with De Morsier syndrome may have important implications for management. The combination of GH deficiency and premature puberty may allow an apparently normal growth rate but with an inappropriately advanced bone age resulting in impaired final stature. GnRH analogues may be a therapeutic option.

In conclusion, some patients with De Morsier syndrome appear to retain the ability to secrete gonadotrophins in the face of loss of other hypothalamic releasing factors. The migration of GnRH neurons after the development of the midline defect may be an explanation.

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Introduction

Septo-optic dysplasia was described by De Morsier in 1956 (1) in nine patients who had absence of the septum pellucidum in association with hypoplasia of the optic nerves. Hoyt *et al.* in 1970 (2) described pituitary dysfunction in association with this syndrome. It is now appreciated that two out of the three features of optic nerve hypoplasia, absence of the septum pellucidum and hypopituitarism, are required to satisfy the diagnosis (3). As the absence of the septum pellucidum is not essential for this syndrome, the older term of De Morsier syndrome may be more appropriate. The endocrinopathy of this condition ranges from isolated growth hormone (GH) deficiency to panhypopituitarism including posterior pituitary dysfunction. An evolving endocrinopathy is common (3) with loss of endocrine function as a sequence in time. In any lesion of the hypothalamo–pituitary axis, irrespective of whether it is idiopathic or due to a destructive lesion, the most common endocrinopathy is insufficiency of GH and gonadotrophin secretion, which occurs before thyrotrophin-releasing hormone (TRH)/thyrotrophin (TSH) or corticotrophin-releasing hormone (CRH)/adrenocorticotrophin (ACTH)

insufficiency (4). Diabetes insipidus is usually secondary to either a destructive hypothalamic pituitary lesion (such as Langerhans' cell histiocytosis or a pituitary tumour) or to a structural abnormality such as De Morsier syndrome (5).

Patients and methods

We have a total of 25 patients with septo-optic dysplasia, of whom 13 are prepubertal. Five patients had delayed puberty with low gonadotrophins, while seven had normal gonadotrophin secretion in the face of deficiencies of other pituitary hormones.

We describe these seven patients (four female, three male), all of whom had at least two out of the three features required for a diagnosis of septo-optic dysplasia. The clinical data are given in Table 1. Patients 1–4 had panhypopituitarism and yet normal gonadotrophin secretion; one of these also had anti-diuretic hormone (ADH) insufficiency. One boy (Patient 1) had initial pubertal delay requiring induction of puberty with depot testosterone treatment but later progressed through puberty normally with a gradual increase in

Table 1 Clinical and neuroradiological findings in seven patients with De Morsier syndrome.

Patient no.	Sex	Age at diagnosis (years)	Age at onset of puberty		Optic nerve hypoplasia*	MRI/CT scan abnormalities
			CA	BA		
1	M	11.0	12.8	9.4	+	No abnormality
2	F	8.5	11.7	10.6	—	Absent septum pellucidum
3	F	0.2	10.3	10.0	+	Absent septum pellucidum, hypoplastic optic nerves
4	M	0.1	10.1	9.1	+	Partial septum pellucidum
5	F	4.5	11.4	10.3	+	Absent septum pellucidum, small optic chiasm
6	F	0.5	9.5	9.6	+	Absent septum pellucidum
7	M	8.0	14.0	8.3	+	No abnormality

*+ represents the presence of optic nerve hypoplasia.
CA = chronological age; BA = bone age.

testicular volume. Patients 4–7 had ‘isolated’ GH deficiency but entered puberty at least a year earlier than would have been expected for their bone age. All four girls entered puberty spontaneously, at a relatively early timing.

Hypothalamo–pituitary function was tested using either insulin-induced hypoglycaemia or glucagon stimulation combined with TRH and gonadotrophin-releasing hormone (GnRH) by standard techniques (6). All patients had varying degrees of hypopituitarism as described in Table 2, but had normal gonadotrophin secretion, with an appropriate rise of serum luteinising hormone (LH) and follicle-stimulating hormone (FSH) to stimulation with intravenous GnRH (Table 2). The normal ranges for age and sex are given in the *Handbook of Endocrine Investigations in Children* (6). Bone age was assessed by the method of Tanner *et al.* (7).

Discussion

Patients who develop an evolving hypothalamo–pituitary endocrinopathy have a typical sequence of loss of anterior pituitary function, which usually commences with loss of the GH axis followed by GnRH/gonadotrophin secretion. In any progressive and evolving anterior pituitary lesion it is extremely unusual to lose

CRH/ACTH and TRH/TSH secretion and yet retain gonadotrophin secretion. Our patients illustrate the retention of gonadotrophin secretion from the anterior pituitary despite panhypopituitarism. Indeed, an early timing of the onset of puberty has been described in septo-optic dysplasia, resulting in precocious/premature puberty (8). This is extremely unusual in children with isolated GH deficiency, where puberty is usually significantly delayed (9, 10).

Children with septo-optic dysplasia may lose height potential due to the combination of GH deficiency producing a reduced growth velocity and precocious/premature puberty permitting an increased rate of epiphyseal closure. Such children therefore need not only careful monitoring of their growth rate, but also their pubertal development and bone maturation; where it is appropriate treatment with a GnRH analogue may be necessary in addition to GH treatment. This is an analogous situation to children with acute lymphoblastic leukaemia, developing GH deficiency and precocious/premature puberty secondary to low-dose cranial irradiation (11).

GnRH neurons differentiate in the nasal mucosa in the roof of the mouth and migrate to the hypothalamus in early fetal life (12). It has been demonstrated that this migration is completed at approximately 13 weeks in

Table 2 Endocrine findings in seven patients with De Morsier syndrome.

Patient no.	Sex	Endocrine findings*					GnRH stimulation (B/S)	
		GH	ACTH	TSH	LH/FSH	ADH	LH (U/I)	FSH (U/I)
1	M	—	—	—	+	+	0.5/5.1	0.6/2.9
2	F	—	—	—	+	—	1.3/2.0	1.0/5.4
3	F	—	—	—	+	+	1.3/6.2	1.7/2.4
4	M	—	—	—	+	+	1.4/10.6	1.1/1.5
5	F	—	+	+	+	+	0.6/5.0	0.7/12.0
6	F	—	+	+	+	+	5.0/17.5	7.3/10.1
7	M	—	+	+	+	+	2.7/20.0	1.1/2.1

*— represents absence of hormone secretion.
B/S = basal and stimulated levels of LH and FSH.

the human fetus (13). In Kallman syndrome there is an association of hypogonadotrophic hypogonadism with anosmia. The X-linked form of the condition has been found to be due to a gene located at Xp22.3 (14, 15). The KAL gene encodes for a protein which appears to be involved in GnRH neuron migration (16). This gene defect has not been detected in patients with septo-optic dysplasia.

The central nervous system midline developmental insult which results in septo-optic dysplasia develops between the 5th and 8th week of pregnancy (17, 18). We hypothesise that the arrival of GnRH neurons in the hypothalamus after the development of a midline defect explains how GnRH secretion may be normal while secretion of other hypothalamic releasing factors is deficient. Moreover, the abnormal hypothalamo-pituitary anatomy may alter the normal suppression of GnRH neuron function and permit an earlier timing of the increase in gonadotrophin secretion, which results in premature/precocious puberty.

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