

ORIGINAL ARTICLES

Endocrine function and morphological findings in patients with disorders of the hypothalamo-pituitary area: a study with magnetic resonance

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Abstract

Evaluation of the sellar area was performed with magnetic resonance imaging in 101 patients (age range 0-8-27 years) with hypopituitarism, isolated diabetes insipidus, hypogonadotrophic hypogonadism, and central precocious puberty. The hypopituitary patients (n=70) included multiple pituitary deficiency (n=23), pituitary deficiency with diabetes insipidus (n=5), and isolated growth hormone deficiency (n=42). The patients with multiple pituitary deficiency showed pathological morphological findings in all cases, with stalk and posterior lobe always involved. The group with associated diabetes insipidus had abnormal stalk in four of five cases and posterior lobe not visible in all cases. Only five of 42 (12%) patients with isolated growth hormone deficiency had abnormalities of the sellar area. In two out of four patients with isolated diabetes insipidus posterior lobe was not seen. All patients with hypogonadotrophic hypogonadism (three with Kallmann's syndrome, one Prader-Willi syndrome, and two idiopathic hypogonadism) appeared normal. In precocious puberty (n=21) the three patients with onset of symptoms before age 2 years exhibited a hypothalamic hamartoma, whereas in the others with onset of puberty between age 2 and 7 the magnetic resonance image was normal in 17 of 18 patients.

The probability of finding a pathological magnetic resonance image was considerably high in our patients with multiple pituitary deficiency, isolated diabetes insipidus, and precocious puberty with very early onset of symptoms. On the contrary, purely functional abnormality is suggested in most patients with isolated growth hormone deficiency, hypogonadotrophic hypogonadism, and precocious puberty with later onset of symptoms.

When a diagnosis of endocrine disorder involving the hypothalamo-pituitary axis is made through functional testing, it is impossible to know whether the defect has an anatomical basis. Magnetic resonance imaging has proved to be the best technique to visualise the sellar and juxtaseellar area and it has been used successfully to evaluate children with hypopituitarism, diabetes insipidus, or other disorders in this area.¹⁻³ In particular the pituitary gland and stalk are clearly seen, even if the association between neuroradiological findings on one hand and type or severity of endocrine

alteration on the other has not yet been clarified. In order to investigate this matter further, the sellar area of 101 patients with various endocrine disorders was studied with magnetic resonance.

Patients and methods

We examined 101 patients (56 males and 45 females; age range 0-8-27 years) with the following endocrine disorders: hypopituitarism, isolated diabetes insipidus, hypogonadotrophic hypogonadism, and central precocious puberty.

(1) HYPOPITUITARISM

All patients (n=70) had short stature (below 3rd centile) at time of diagnosis and showed growth hormone deficiency (growth hormone concentration peak <8 µg/l after pharmacological tests and mean growth hormone concentration during night profile <3 µg/l). No patients had a positive history for postnatal head trauma, intracranial tumour, or brain infection. All patients received replacement treatment with pituitary or recombinant human growth hormone. Six patients had stopped taking growth hormone at the time of the examination.

A perinatal history was obtained from the parents or from case records.

These patients were subdivided into the following three groups:

(a) Multiple pituitary deficiency

There were 23 cases (20 males and three females; mean (SD) age 18.3 (4.6) years, range 11.8-27) of whom 17 had adrenocorticotrophic hormone deficiency, 21 thyrotrophin releasing hormone deficiency (protracted or delayed thyroid stimulating hormone response to thyrotrophin releasing hormone with peripheral thyroid deficiency during follow up), and 19 certain gonadotrophin deficiency. All subjects were having appropriate replacement treatment: hydrocortisone acetate for adrenocorticotrophic hormone deficiency, thyroxine for thyroid stimulating hormone deficiency, and human chorionic gonadotrophin and/or testosterone enanthate for gonadotrophin deficiency.

(b) Pituitary deficiency with diabetes insipidus

There were five cases (four males and one female, range 6-15 years). All patients had idiopathic diabetes insipidus and one patient also had thyroid stimulating hormone deficiency. Diabetes insipidus was treated with synthetic antidiuretic hormone, desmopressin (DDAVP, Ferring).

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(c) Isolated growth hormone deficiency

There were 42 cases (25 males and 17 females, mean (SD) age 11.6 (3) years, range 5.4–17.9).

(2) ISOLATED DIABETES INSIPIDUS

There were four cases (one male and three females, range 0.8–19 years). All cases suffered from idiopathic diabetes insipidus and were having replacement treatment.

(3) HYPOGONADOTROPHIC HYPOGONADISM

There were six cases (five males and one female, age range 14–16 years) including three patients with Kallmann's syndrome (age 14.8, 15.8, and 16 years), one patient with Prader-Willi syndrome (15.4 years), and two with idiopathic hypogonadotrophic hypogonadism (14 and 15 years). They had not received any previous treatment.

(4) PRECOCIOUS PUBERTY

There were 21 cases (20 females and one male, mean (SD) age 7.5 (3.1) years; age range 0.8–11.2). All cases started puberty before age 7 years and all but two were on treatment with synthetic luteinising hormone releasing hormone analogue (buserelin).

For magnetic resonance a 0.5 T magnet was used in all patients (Philips Gyroscan) with sagittal and coronal images of 2.5 mm slice thickness. Images were obtained with T1

weighted sequences (TR 364 msec, TE 30 msec) and T2 weighted sequences (TR 1500 msec, TE 50/100 msec). The height of the anterior lobe was measured on the sagittal T1 weighted image, using a cursor on the display. A height of less than 2 mm was considered as an indication of small pituitary gland.^{4,5} Sedation was necessary in eight patients.

Results**(1) HYPOPITUITARISM**

All patients with multiple pituitary deficiencies, with or without diabetes insipidus, presented abnormalities of the pituitary or of the stalk.

(a) Multiple pituitary deficiency (table 1)

The stalk was mainly involved: clearly transected in 10 cases (fig 1) and not seen in the remaining 13 cases. The posterior lobe was ectopic at the proximal stump in the 10 patients with transected stalk and in seven other patients. Six patients did not show the characteristic high signal intensity of the posterior lobe. The anterior lobe was abnormal in 16 patients: small in three cases (height of 1.9, 1.5, 1.8 mm) and not seen in the remaining 13 cases; in five of the latter the sellar area was partially or completely filled with cerebrospinal fluid (empty sella). Mean (SD) anterior lobe height in the seven cases with pituitary >2 mm was 3.6 (2.4) mm. There was no correlation between height of the anterior lobe and duration of replacement treatment. Two patients had agenesis of the corpus callosum and one hypogenesis of cerebellar vermis.

In 12 patients (52%) a clear history of adverse perinatal events was found (breech delivery in seven cases, asphyxia in five cases); these subjects did not differ from the others concerning magnetic resonance findings and type of hormonal deficiency. Similarly, the seven subjects with anterior lobe >2 mm (table) did not differ from the others for either the type of hormonal defect or the presence of adverse perinatal events (four out of seven).

(b) Pituitary deficiency with diabetes insipidus (table 2)

In all cases the posterior lobe was not seen. The stalk was not visible in four cases. The patient with growth hormone and thyroid stimulating hormone deficiency had the sella fully filled with cerebrospinal fluid (empty sella). One patient had an anterior lobe of 1.3 mm. No patients had a positive history for adverse perinatal events.

Table 1 Magnetic resonance findings in the 23 patients with multiple pituitary deficiency without diabetes insipidus

No of patients	Anterior lobe	Stalk	Posterior lobe
5	<2 mm	Transected	Ectopic
5	Normal	Transected	Ectopic
1	Normal	Not seen	Ectopic
3	<2 mm	Not seen	Ectopic
1	Normal	Not seen	Not seen
3	<2 mm	Not seen	Not seen
3	Sella partially filled with cerebrospinal fluid		Ectopic
2	Sella filled with cerebrospinal fluid		Not seen

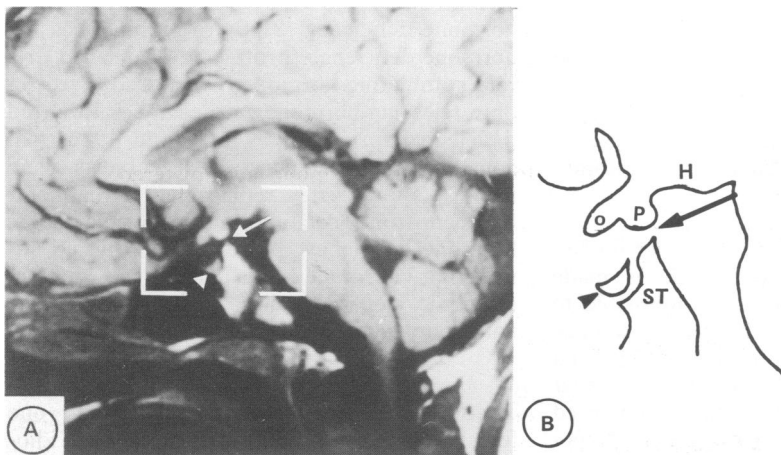


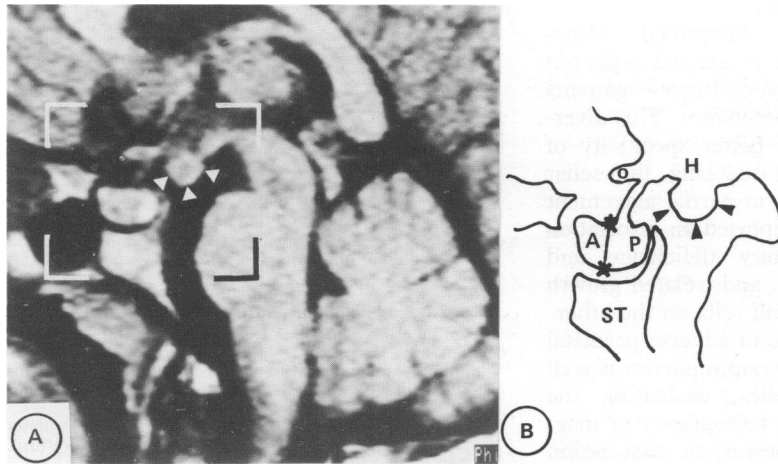
Figure 1 Sagittal magnetic resonance image (A) and line diagram (B) illustrating a hypopituitary patient with multiple deficiency: the stalk is transected (arrow), the bright signal of the posterior lobe (P) is absent in the sella and appears to be present in the median eminence of the hypothalamus. The anterior lobe (arrowhead) is small in height (1.9 mm). Normal appearance of the hypothalamus (H); o: optic chiasm, ST: sella turcica).

Table 2 Magnetic resonance findings in the five patients with pituitary deficiency and diabetes insipidus

No of patients	Anterior lobe	Stalk	Posterior lobe
3	Normal	Not seen	Not seen
1	<2 mm	Normal	Not seen
1	Sella filled with cerebrospinal fluid		Not seen

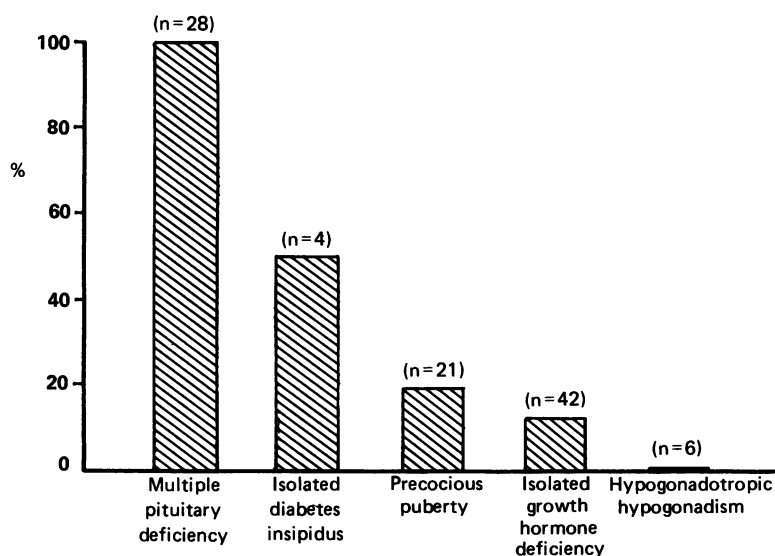
Table 3 Magnetic resonance findings in the 42 patients with isolated growth hormone deficiency

No of patients	Anterior lobe	Stalk	Posterior lobe
37	Normal	Normal	Normal
1	<2 mm	Transected	Ectopic
3	<2 mm	Normal	Normal
1	Sella filled with cerebrospinal fluid		Not seen

**Figure 2** Sagittal image (A) and line diagram (B) of a patient with hypothalamic hamartoma (arrowheads). The stalk, the anterior lobe (A) and posterior lobe (P) are normal. Anterior lobe height (cross) is 8.3 mm.**Table 4** Mean (SD) anterior lobe height (mm) in three groups of patients with anterior lobe height >2 mm

Isolated growth hormone deficiency (n=37)	4.95 (1.03)
Precocious puberty (n=21)	6.25 (1.20)*
Hypogonadotrophic hypogonadism (n=6)	6.55 (1.46)**

*p<0.025 compared with isolated growth hormone deficiency.
**p<0.001 compared with isolated growth hormone deficiency.

**Figure 3** Percentages of pathological magnetic resonance findings in the groups of patients studied.

(c) *Isolated growth hormone deficiency* (table 3) Only five patients (12%) showed abnormalities of the sellar area. One had an empty sella, one a transected stalk with anterior lobe <2 mm and ectopic posterior lobe, and three had the anterior lobe <2 mm. Twelve patients (29%) had a

certain history of adverse perinatal events. Mean (SD) anterior lobe height in the 37 patients with pituitary >2 mm was 4.95 (1.03).

(2) *Isolated diabetes insipidus*

Of the four patients two cases were normal, in one the posterior lobe was not visible, and in one neither the posterior lobe nor the anterior and the stalk were visible.

(3) *Hypogonadotrophic hypogonadism*

All six patients showed a normal hypothalamus and pituitary. Mean (SD) pituitary height was 6.55 (1.46) mm.

(4) *Precocious puberty*

The stalk was faint in only one patient, whereas three patients (14%) had a hypothalamic hamartoma (fig 2); these three patients had the first symptoms before age 2 years.

Mean (SD) pituitary height was 6.25 (1.2) mm. Comparisons between mean pituitary heights in patients with anterior lobe >2 mm are shown in table 4.

Discussion

The examination of the sellar area with this precise, safe technique enabled the observation of a number of morphological features in the pathological conditions studied.

The probability of pathological morphological findings is highest in patients with multiple pituitary deficiency, with or without diabetes insipidus, and lowest in the patients with hypogonadotrophic hypogonadism (fig 3). All our subjects with multiple pituitary deficiency had a pathological magnetic resonance image, with the stalk mainly involved, in accordance with the reports of other authors.^{2 6 7} The morphological findings are consistent with suprahypophysal damage, as suggested by dynamic tests with releasing factors, growth hormone releasing hormone, and thyrotrophin releasing hormone.^{8 9} It is interesting to note that all our patients with associated thyroid deficiency, showing abnormalities of the stalk in all cases, had an abnormal thyroid stimulating hormone response to thyrotrophin releasing hormone. These data confirm that deficient thyroid function in hypopituitarism with growth hormone treatment is due to anatomical damage and not to the growth hormone administered.¹⁰

In our study, there is no clear association between height of the anterior lobe and function of the gland. In particular, unlike Kikuchi *et al*,⁶ not all subjects with pathological thyroid stimulating hormone response to thyrotrophin releasing hormone had a 'small-sized' pituitary gland. Furthermore, the patients with isolated growth hormone deficiency (table 4) showed a pituitary height lower than that of the patients with precocious puberty or hypogonadism. As the latter are hypogonadotrophic, the difference in height between the patients with isolated growth hormone deficiency and the other two groups would seem to depend on a different degree of somatotroph activity.

The lack of the posterior lobe visualisation in six patients without diabetes insipidus (table 1), may be related to the normal temporal variation of the intensity of the bright signal, possibly reflecting differing physiological and stress states of patients, as recently described.¹¹

A high percentage (88%) of normal magnetic resonance images was found in the subjects with isolated growth hormone deficiency, suggesting purely functional damage.

Unlike findings on computed tomography,^{12 13} an empty sella is unusual (eight out of 70, 11%) in our hypopituitary patients examined with magnetic resonance. This diversity might be related to better specificity of magnetic resonance in visualising the sellar content. Our findings are in partial agreement with Surtees *et al*, who reported an association between multiple pituitary deficiency and empty sella, on one hand, and isolated growth hormone deficiency and full sella on the other.

The increased incidence of adverse perinatal events in children with hypopituitarism is well known.^{14 15} Recent studies, evaluating the sellar area with computed tomography or magnetic resonance, hypothesise an association between neonatal insult and pituitary anatomical damage. Our data cannot be conclusive on this matter. In fact only 52% of our patients with multiple pituitary deficiency and evident morphological damage have a positive history for adverse perinatal events. This seems to indicate that mechanical or hypoxic perinatal insults cannot be the primary aetiological factor.

Two out of four patients with isolated diabetes insipidus had a visible posterior lobe. Even if this might not seem in agreement with Fujisawa *et al*,³ who stated that a normal posterior lobe is equivalent to functional integrity, the possibility of an extra hypophyseal receptor defect as a cause of diabetes insipidus should be considered.¹⁶

Finally, in the patients with hypogonadotropic hypogonadism, with or without anosmia, and in 17 out of 18 patients with precocious puberty and onset of symptoms after age 2, magnetic resonance did not identify morphological abnormalities, again indicating a functional defect. On the contrary, in the patients with precocious puberty and very early onset of symptoms (three out of three), a clear

abnormality was found (hypothalamic hamartoma), as our previous data provided by computed tomography showed.¹⁷

In conclusion, magnetic resonance imaging is particularly useful in defining the morphological aspects of the hypothalamo-pituitary region in various endocrine disorders. However, it does not show a constant association between functional endocrine deficiency and neuroradiological abnormalities.

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