

Short report

Syndrome of cerebellar ataxia and hypogonadotrophic hypogonadism: evidence for pituitary gonadotrophin deficiency

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SUMMARY Familial cerebellar ataxia with hypogonadotrophic hypogonadism is a rare condition. Two affected siblings in a sibship of three were studied and found to have low plasma gonadotrophin levels. No rise in gonadotrophin levels was demonstrable after repeated stimulation with LHRH. The pattern of TSH and prolactin responses to TRH stimulation suggest hypothalamic dysfunction. The results clearly identify the cause of hypogonadism to be due to a defect in production or release of gonadotrophins by the pituitary gland and suggest that hypogonadism is part of a greater endocrine disturbance involving both the hypothalamus and pituitary.

The association of spino-cerebellar degeneration of the nervous system with endocrine dysfunction is well established. Holmes¹ first described a family of eight siblings in whom four members with cerebellar ataxia were noted to be sexually undeveloped. Except for one report,² the endocrine status of such patients has been poorly documented. We describe the investigations performed which establish the cause of hypogonadism to be due to a defect in the pituitary.

Case report

Case 1

An 18 year old Chinese male presented with unsteadiness of gait. His birth and developmental history were normal till the onset of ataxia at 8 years of age. He was the youngest of three siblings from a non-consanguineous marriage. On examination, he was found to be pre-pubertal. He was 166 cm in height and had eunuchoid proportions. He was sexually undeveloped with absent facial and pubic hair. The testicular volumes were 1 ml bilaterally. There was gaze-dependent nystagmus, with limb and truncal ataxia and pendular knee jerks. Fundoscopy revealed peri-papillary degeneration with chorio-retinal atrophy. The optic discs were normal with high

myopia and astigmatism. No sensory deficits or pyramidal release were detected. CT of the brain revealed uniform atrophy of the cerebellar hemispheres. The fourth ventricle was dilated consequent upon the atrophy (fig). The pituitary fossa, cervical spine and base of skull were normal. Conduction velocities over median, ulnar and common peroneal nerves were normal. The electrocardiogram and karyotype were normal.

Endocrinological studies

The results showed a hypogonadotrophic hypogonadism. (table) The LH and FSH responses to a 100 µg dose of LHRH were subnormal. This was followed by twice-daily intramuscular injections of 100 µg LHRH (Relefact[®]—Hoechst AG, Germany) for 7 days. A second LHRH stimulation was performed at the end of the 7 days under similar conditions. Gonadotrophin assays were quantified in duplicate by radio-immunoassay using commercial kits (Pharmacia Diagnostics AB, Uppsala Sweden).

Case 2

A 21 year old Chinese female (sister of Case 1) was seen for primary amenorrhoea and ataxia. Her birth and developmental history were normal till the onset of unsteadiness at 6 years of age. On examination she was found to be pre-pubertal with eunuchoid proportions. She was 156 cm in height with an upper to lower segment ratio of 0.85, and an arm span of 169 cm. The patient was sexually undeveloped with no secondary sexual hair or breast development. Gynaecological examination revealed a small vagina with clinically undetectable cervix, uterus and adnexal structures. There was limb and truncal ataxia with scanning speech,

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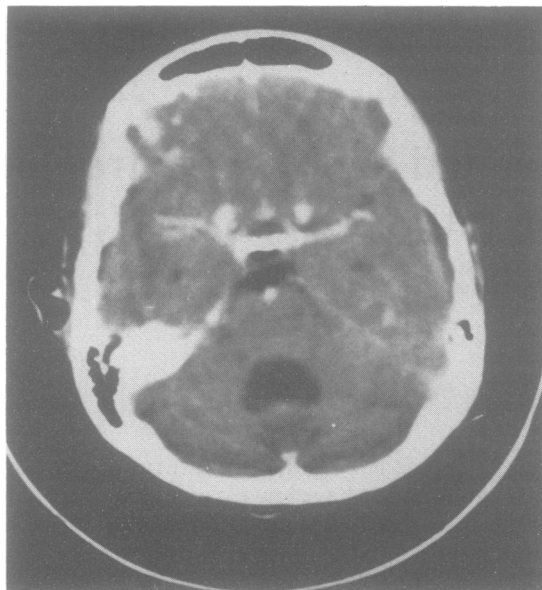


Figure CT scan of Case 1 showing dilatation of the fourth ventricle consequent upon cerebellar atrophy.

nystagmus and pendular knee jerks. Sensory deficits or pyramidal release were not detected. CT of the brain revealed bilateral cerebellar atrophy with a dilated fourth ventricle and a normal pituitary fossa. The karyotype was 46XX. Pelvic ultrasound revealed agenesis of the uterus and adnexal structures. Endocrinological studies revealed hypogonadotrophic hypogonadism. The 17-beta oestradiol was less than 11 pg/ml (normal 48–350) while the LH was less than 2 IU/l (normal 5–24) and the FSH 1.3 IU/l (normal 4–12). The serum prolactin level was 6.7 ng/dl (normal 5–27.7).

Discussion

The heredo-familial ataxias are a heterogeneous category of degenerative disorders involving the

nervous system.³ There are several variants, of which Friedreich's ataxia⁴ is the most well known. A predominantly cerebellar form,⁵ the type found in our patients, is another variant.

In 1907 Holmes¹ first reported an association between cerebellar ataxia and sexual undevelopment. It is now known that the ataxia-hypogonadism syndrome occurs in two forms. One is the association of ataxia with hypergonadotrophic hypogonadism, of which there are several reports.^{6–8} The most commonly identified cause of hypergonadotrophic hypogonadism appears to be Klinefelter's syndrome.^{7,8} The other variety associates cerebellar ataxia with a hypogonadotrophic form of hypogonadism. This has been reported by several authors^{9–12} who found low levels of urinary gonadotrophins in the cases studied, presumably from disease of the hypothalamus or pituitary.

Berciano² provided the first evidence for a hypothalamic defect by demonstrating an increase in gonadotrophin levels after repeated stimulation with LHRH, pointing to a deficiency in hypothalamic stimulating factor.

The clinical features of our propositi are virtually identical to those described by Berciano.² However, our results were dissimilar. The absence of a rise in LH and FSH after repetitive stimulation with LHRH points to a defect in pituitary production or secretion of gonadotrophins. The absence of lesions in the pituitary and hypothalamus on CT of the brain corroborates our postulation that the defect is a functional one rather than a structural one.

There is also evidence to suggest that the defect is not confined to the pituitary but involves the hypothalamus as well. The TSH and prolactin responses to TRH stimulation at 60 minutes are higher than those at 20 minutes (table). This pattern of responses is presumptive evidence of hypothalamic dysfunction.

There was impairment of GH release despite

Table Baseline hormonal profile and results of combined GnRH and TRH stimulation, insulin tolerance tests

| Time (min) | 0' | 20' | 30' | 40' | 60' | Normal range (Basal) |
|--------------------|------|------|-----|-----|------|----------------------|
| LH | 3.3 | 3.4 | — | — | 3.3 | 5 – 16 mU/l |
| FSH | 2.4 | 2.4 | — | — | 3.5 | 3 – 8 mU/l |
| LH* | 2.6 | 3.0 | — | — | 2.5 | 5 – 16 mU/l |
| FSH* | 2.9 | 4.0 | — | — | 4.1 | 3 – 8 mU/l |
| TSH | 1.8 | 11.8 | — | — | 18.3 | 0.5 – 5.0 mU/l |
| Glucose | 97 | 44 | 10 | 10 | 35 | |
| GH | 0.4 | 0.3 | — | 1.5 | 1.9 | <0.5 – 2.3 ng/ml |
| Prolactin | 8.1 | 16.3 | — | — | 24.5 | 5.0 – 27.7 ng/dl |
| Total Thyroxine | 6.9 | | | | | 4.2 – 12 µg/dl |
| Cortisol 0800 h | 13.7 | | | | | 8 – 23 µg/dl |
| 2400 h | 3.5 | | | | | 3 – 10 µg/dl |
| Osmolality† Plasma | 288 | | | | | 275 – 305 mOsm/kg |
| Urine | 654 | | | | | > 600 mOsm/kg |

Stimuli used were IV 100 µg TRH, 100 µg LHRH & Neutral Insulin 0.1 U/kg body weight.

*Following seven days of twice daily intramuscular 100 µg LHRH.

†Samples at 0800 h following overnight water deprivation.

marked hypoglycaemia. An intact hypothalamo-pituitary axis is a pre-requisite for normal GH release. The impaired response in this patient may be due to a defect in the pituitary or the hypothalamus or both. GHRH stimulation may resolve the issue; poor GH response to GHRH would indicate a defect in the pituitary.

We conclude that the syndrome of ataxia and hypogonadotropic hypogonadism is not a homogeneous entity. Pituitary deficiency is not isolated to gonadotrophins and there is evidence suggesting hypothalamic dysfunction. It appears that the endocrine disturbance in this syndrome is a spectrum which involves both the hypothalamus and pituitary.

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