Henry Ford Hospital Medical Journal

Volume 35 | Number 4 Article 3

12-1987

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Hypothalamic Hypogonadotropic Hypogonadism in an Adolescent Male: A Rare Manifestation of Aqueductal Stenosis

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Congenital stenosis of the aqueduct of Sylvius accounts for most cases of hydrocephalus diagnosed during infancy and early childhood (1,2). Enlargement of the skull and progressive neurological symptoms early in life usually suggest the diagnosis (2). With lesser degrees of obstruction, the disorder may not become apparent until adolescence or adulthood (2,3). Decompensation of the hydrocephalus is heralded by a symptom complex which includes intellectual impairment, headaches, visual disturbances, seizures, and unsteady gait (3-6). Approximately one half of the patients will have papilledema at presentation (3,4). Reduction of the hydrocephalus by ventricular cerebrospinal fluid (CSF) shunt procedures can alleviate the neurologic abnormalities (3,4,6).

Although the presence of neuroendocrine abnormalities in a small subset of adolescent or adult patients with aqueductal stenosis has been reported (2-5,7,8), aqueductal stenosis presenting as pure endocrine dysfunction without neurologic abnormality has been only sporadically described in the literature (9-11). No reports have detailed a male presenting in this latter fashion. The endocrine abnormalities are ascribed to hypothalamic-pituitary dysfunction resulting from pressure on the hypothalamus exerted by the expanded end of the third ventricle (12). Pituitary function is usually restored by ventricular CSF shunt procedures (9,11).

We report a case of an adolescent male with aqueductal stenosis whose presenting complaints were short stature and pubertal arrest, without neurologic abnormalities. Hormone testing demonstrated partial hypopituitarism secondary to hypothalamic dysfunction. Decompression of the hydrocephalus reversed the clinical and laboratory abnormalities.

Case Report

A 17-year-old white male was referred to us for evaluation of arrested pubertal development and decelerating linear growth. His growth and development had been normal until age 10. His attenuated growth, shown by a deviation from his centile channel for height, was first detected at age 13 (Fig 1). By age 16 he had stopped growing, and his height was markedly below normal. Initial pubertal changes occurred at age 13, but had not progressed beyond scant axillary and pubic hair growth. He felt well, was physically active, and received average grades in a school class appropriate to his age. He denied headaches, seizures, visual disturbances, or clumsiness.

The patient was mildly obese, appeared prepubertal, was 158 cm tall, and weighed 43.5 kg. He was normocephalic and had normal pupils and optic fundi. Genitalia (testicular length 2 cm) and axillary and pubic hair were Tanner Grade II. The results of the neurological examination, including Goldmann visual fields, were normal. Skeletal age, as interpreted from hand radiographs, was consistent with the standards for a 14-year-old boy.

Because the patient's puberty began normally then ceased prematurely, and because his short stature had resulted from a deceleration in linear growth, an acquired disorder was suspected. The differential diagnosis included hypothyroidism, Cushing's syndrome, and hypopituitarism.

Endocrine testing data excluded hypothyroidism, Cushing's syndrome, and growth hormone deficiency. The data, however, revealed that his testosterone concentration was low and that his luteinizing hormone secretion responded briskly to gonadotropin-releasing hormone (Table). These results demonstrated that his pituitary gland was intact and suggested that the secretion of gonadotropin-releasing hormone from his hypothalamus was impaired, resulting in hypothalamic hypogonadotropic hypogonadism.

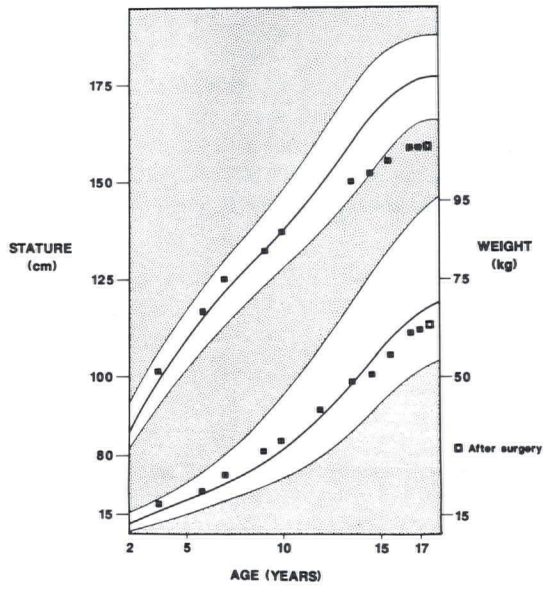

Fig 1—Cumulative growth chart showing curve of attenuated growth with growth arrest and short stature, and changes in body weight.

Submitted for publication: January 29, 1987.
Accepted for publication: February 13, 1987.
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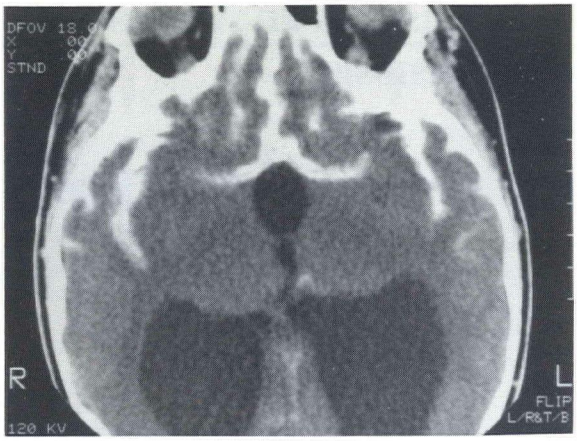

Fig 2—Computed tomography of brain (transverse section) at the level of the sella demonstrates ballooning of the third ventricle into the sella.

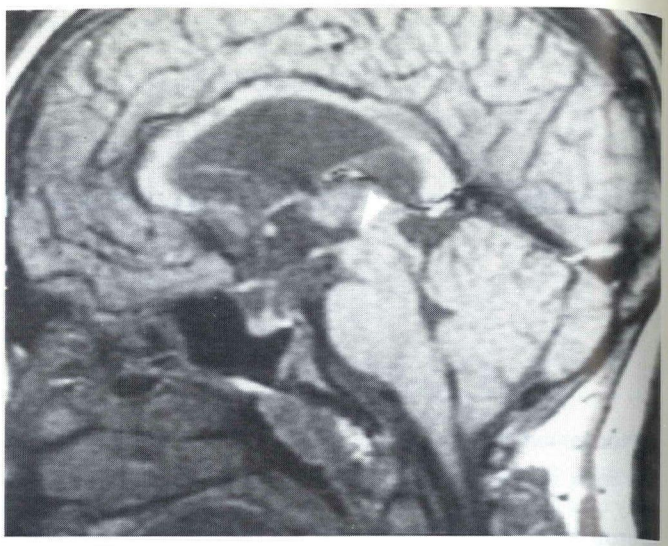

Fig 3—Nuclear magnetic resonance of the head (midline sagittal section) reveals the stenotic proximal portion of the aqueduct of Sylvius (arrow) with enlarged third ventricle and a normal-sized fourth ventricle.

Computed tomography of the head was performed to detect a suprasellar mass such as a craniopharyngioma. It revealed marked internal hydrocephalus which had distended the lateral and third ventricles and herniated the third ventricle into an enlarged sella turcica (Fig 2). The fourth ventricle was normal, and a mass was not present. High-resolution computed tomography of the sella showed marked thinning and erosion of the floor of the pituitary fossa. Nuclear magnetic resonance imaging excluded the presence of a mass obstructing the aqueduct of Sylvius and showed that the pituitary gland and its stalk were normal (Fig 3). These findings established the diagnosis of hydrocephalus caused by stenosis of the aqueduct of Sylvius. Compression of the hypothalamus by the hydrocephalic third ventricle was postulated as the cause of the patient's arrested growth and puberty.

A ventricular-peritoneal shunt was performed to reduce the hydrocephalus. By five weeks after surgery, the patient had observed an increase in sweating and in facial, axillary, and pubic hair growth. Computed tomography showed a marked reduction of the hydrocephalus. Ten weeks after surgery, he reported the onset of nocturnal emissions and tender gynecomastia. By three months after surgery, his testicles had increased in size to 3 cm, his pubic hair was classified as Tanner Grade IV, and his height had increased by 1 cm. The ratio of luteinizing hormone to follicle-stimulating hormone had reversed, and serum testosterone levels had increased consistent with pubertal maturation (Table).

Discussion

Aqueductal stenosis presenting in adolescence and adulthood is not rare (2) and has five general groups of presentation: intellectual impairment, headache, seizures, visual disturbance, and gait disturbance (3-7). Concomitant endocrine abnormalities

Table
Endocrine Studies: Preoperative and Postoperative Data

Indice	Preoperative	Postoperative 4 Months	Postoperative 10 Months	Normal Values for Pubertal Male
Testosterone (ng/dL)	30	260	410	300-1,000
Basal LH (μIU/mL)	5	8	—	4-23
LH after 100 μg GnRH (μIU/mL)	44	—	—	increment > 16
Basal FSH (μIU/mL)	7	5	—	1.5-19
Peak growth hormone (ng/mL) after:				
Bromocriptine (2.5 mg)	11	4.7	—	> 7 ng/dL
Insulin (0.1 U/kg)	—	18	—	> 7 ng/dL
Somatomedin-C (U/mL)	1.6	2.3	—	0.9-3.1 (15-18 years)
Prolactin (ng/mL)	13	17	—	< 25
T_4, total thyroxine (μg/dL)	6.8	6.2	6	5-11
Basal TSH (μIU/mL)	1.7	1.2	—	< 7.5
TSH after 100 μg TRH (μIU/mL)	9.2	6.1	—	increment > 6
Plasma AM cortisol (μg/dL)	15	17	—	8-28
DHEA sulfate (ng/dL)	1,300	1,300	1,100	1,990-3,350

LH = luteinizing hormone, GnRH = gonadotropin-releasing hormone, FSH = follicle-stimulating hormone, TSH = thyroid-stimulating hormone, TRH = thyrotropin-releasing hormone, and DHEA = dehydroepiandrosterone.

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such as amenorrhea, delayed or precocious puberty, short stature, obesity, hypothyroidism, and diabetes insipidus have been noted in the older literature. One study reported symptoms suggestive of endocrine defects in 10% of patients presenting with aqueductal stenosis (3), but clearly documented reports of endocrine deficiency are few and mainly describe females with hypothalamic amenorrhea (8-11,13-17). The predilection for endocrine abnormalities in females with aqueductal stenosis is of interest (8) because this condition occurs with about equal frequency in males and females (2-4). Furthermore, the recent literature reveals only three documented cases of endocrine disturbances in adolescent or adult males: one with isolated growth hormone deficiency, a second with gonadotropin deficiency and short stature, and a third with short stature and pubertal delay (12-14). All three presented with neurologic abnormalities that prompted investigation and diagnosis. The endocrine abnormalities were subsequently recognized. In two patients, regression of the endocrine abnormalities occurred following CSF drainage procedures (13,14).

Our patient's case is unusual as he is one of the few males reported to have an endocrine abnormality in the setting of aqueductal stenosis (12-14). Moreover, to the best of our knowledge, this is the first case of aqueductal stenosis in a male who presented with endocrine dysfunction without neurologic abnormality. The investigation of pubertal arrest and short stature in our patient led to the documentation of hypogonadism and culminated in the discovery of aqueductal stenosis. Ventricular-peritoneal shunting has decompressed the hydrocephalus which resulted from the aqueductal stenosis and has led to the reversal of the endocrine abnormality.

Nuclear magnetic resonance imaging in adult patients with aqueductal stenosis has been previously reported (18), but this application in aqueductal stenosis with only endocrine dysfunction is unique. It contributed to an accurate diagnosis in our case by excluding the presence of a tumor compressing the aqueduct.

Unlike patients with communicating hydrocephalus, who rarely have endocrine abnormalities (19), patients with aqueductal stenosis appear to be at risk for these abnormalities. This is because the disproportionate enlargement of the anterior end of the third ventricle leads to pressure-induced dysfunction of the hypothalamic-pituitary axis (12,20). The neural pulse generators of gonadotropin-releasing hormone and growth hormone-releasing hormone are located in the medial hypothalamic neurons and are necessary for normal gonadotropin and growth hormone release (21). In aqueductal stenosis with hydrocephalus, the function of these pulse generators is presumably impaired by pressure from the hydrocephalus.

The preponderance of females in reports of endocrine manifestations of aqueductal stenosis indicates that the female hypothalamic-pituitary-gonadal axis is either more sensitive to hydrocephalus than the male axis or that hypogonadal dysfunction in males may be present but not recognized. The failure of an adolescent female to menstruate or the cessation of menses in a young adult female are dramatic signposts of endocrine dysfunction. Pubertal development in a male lacks such a discrete event heralding the completion of puberty, and signs and symptoms of male hypogonadism may be more easily missed. The serious neurologic abnormalities usually noted at presentation in patients with aqueductal stenosis may further obscure endocrine dysfunction in males.

The lack of neurologic abnormalities in our patient with aqueductal stenosis is noteworthy but unexplained. Only his arrested pubertal development and short stature brought him to medical attention. A plot of the patient's height on growth charts demonstrated a deceleration of linear growth velocity and suggested that the aqueductal stenosis had led to endocrine dysfunction at least four years before we first saw him. Patients with aqueductal stenosis have been reported to remain only mildly symptomatic for extended periods and then suddenly develop symptoms of decompensated hydrocephalus and signs of increased intracranial pressure (22).

The reversal of endocrine abnormalities by ventricular CSF shunting, as demonstrated in our patient, is well recorded (7,9,11,13-15,23,24). This apparently reflects the decompression of the internal hydrocephalus and release of downward pressure on the hypothalamus and pituitary. Reversal of endocrine dysfunction has been documented as early as one month (11) and as late as five years (8) after surgery, with most responses occurring within one year (8,9,14,22).

Our patient responded to surgery with an early and dramatic resumption in pubertal development, paralleled by increases in serum testosterone. His pubertal maturation has continued during the past 11 months since his surgery. His resumption of growth has been less dramatic; no pubertal growth spurt has been noted. While his somatomedin-C levels are adequate, a neurosecretory disorder of growth hormone release may be present. This was suggested after surgery by a failure of growth hormone levels to rise following the administration of bromocriptine. Further observation over time may document a spontaneous increase in growth velocity. However, a trial of growth hormone may be warranted in the future if bone age progresses in the face of suboptimal growth rate.

Conclusions

Decelerating linear growth and arrest of puberty present a challenging differential diagnosis, ranging from treatable idiopathic disorders to reversible specific pathology. We have expanded this differential diagnosis in the male to include aqueductal stenosis. This disorder should be considered in patients of any age who have hypothalamic hypogonadotropic hypogonadism.

Aqueductal stenosis can be readily detected by computed tomography of the brain. Nuclear magnetic resonance imaging improves diagnostic accuracy through its sensitivity in detecting cystic and solid tumors obstructing the aqueduct. Ventricular CSF shunting of the hydrocephalus of aqueductal stenosis can restore normal endocrine function and prevent serious neurologic sequelae of this disorder.

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