Optic Hypoplasia with Pituitary Dwarfism (Kaplan-Grumbach-Hoyt Syndrome, or DeMorsier Syndrome)

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Abstract

A case of a 14-year-old boy with optic hypoplasia and pituitary dwarfism was presented. Eye Examination showed typical hypoplasia of the left optic nerve and mild hypoplasia of the right optic nerve. Except for dwarfism and nystagmus, the appearance of the patient was not unusual. Computed tomography revealed an enlargement of the suprachiasmatic cistern, and the presence of the septum pellucidum. The pituitary function tests revealed complete deficiency in GH, and poor or intermediate secretion in ACTH, TSH, PRL, LH and FSH. Urine volume and specific gravity were normal. Therapy with human growth hormone has been successful. It was indicated that hypopituitarism was probably of hypothalamic origin and early recognition of the syndrome is important in view of the possibility of treating growth retardation in some blind, or near blind children.

DeMorsier (1956) described optic hypoplasia in 9 patients out of 36 patients who lacked the septum pellucidum. He suggested embryological defect and applied the name of septo-optic hypoplasia to these cases. Kaplan et al (1970) reported that among 36 patients with idiopathic pituitary dwarfism, 6 patients had optic dysplasia and midline abnormalities of the prosencephalon. Further cases with septo-optic hypoplasia and pituitary dwarfism were reported by Ellenberger and Runyan (1970), Hoyt et al. (1970), Billson and Hopkins (1972), Brooke et al. (1972), Harris and Haas (1972), Patel et al. (1975), Toublanc et al. (1976), Fukushima et al. (1978), Huseman et al. (1978), Lovrenčić et al. (1978) and Frish and Schober (1980). These reports indicated that an embryonal malformation caused anatomical abnormalities of the prosencephalon and functional disturbances of the pituitary grand. Today, the association of optic hypoplasia with hypopituitarism is called DeMorsier syndrome (Harris and Haas, 1972; Huseman et al., 1978; Frish and Schober, 1980) or Kaplan-Grumbach-Hoyt syndrome (Toublanc et al., 1976; Lovrenčić et al., 1978).

The purpose of this study is to present another patient with the syndrome, a boy who has been successfully treated with human growth hormone (hGH). Since the condition with blindness, or near blindness, from birth, and slow somatic development may be not so rare, it is important to call additional attention to the syndrome.

Case Report

The boy was born in 1968 and at the time of first examination he was 8 and 2/12 yrs. There was no consanguinity in the family,
Fig. 1. Height growth of the patient. Height plotted at chronological age (●) and at skeletal age (○). Shadow shows the range (M-SD) in normal Japanese boys.

No other members of the family are of small stature or have endocrine disease. His mother was a 24-yrs primipara. The gestation was normal and his mother took no medicine during the pregnancy. He was born at term and the delivery was normal. The birthweight was 3,580 g. His walking without support at the age of 1 and 3/12 yrs was normal. Blindness of the left eye was discovered at the age of 4 yrs. Gradually he developed small stature with a relatively normal body weight compared to each height age (Fig. 1). At the age of 1 and 5/12 yrs, 3 and 10/12 yrs, 4 and 10/12 yrs, 5 and 10/12 yrs, and 6 and 10/12 yrs, his height was 71.8 (mean value for Japanese boys, 80.1) cm, 85.3 (98.9) cm, 88.5 (105.2) cm, 92.7 (110.1) cm and 96.2 (116.6) cm, respectively.

At the first examination, his height was 101.6 (123.8) cm and weight was 16.0 (15.9) kg. Consciousness was clear and intelligence was normal. There was no motor or sensory disturbance. Minor anomalies like cleft lips or palate, saddle nose or frontal bossing were not seen. Laboratory studies revealed normal values for serum electrolytes, urinalysis, haematological studies and liver function. Radiographic examination of the chest and skull showed no abnormality. A bone age of 2 and 8/12 yrs was determined according to the atlas of Greulich and Pyle (1959). The karyotype of peripheral leukocytes was 46 XY with no structural abnormality.
Endocrinological Findings

The results of endocrinological studies at his age of 8 yrs are shown in Table 1. The diagnosis of pituitary dwarfism was confirmed by the complete lack of GH responses to arginine (0.5 g/kg, iv), insulin (0.1 IU/kg), 1-DOPA (250 mg, per os)+propranolol (10 mg, per os) and glucagon (1 mg, im)+propranolol. Serum TSH to TRH (500 µg, iv) showed a delayed response. Thyroid function tests were normal. Basal urinary 17 OHCS and the maximum value to Metopirone (2 g, per os) were decreased. The basal serum PRL concentration was normal but the response to TRH was slightly abnormal.

The results of endocrinological studies when he was 12 yrs old are shown in Table 2. He had a completely infantile genitalia and no pubic hair, both of which were rated as stage I according to Marshall and Tanner (1970). The testicular volume was assessed at 0.8 ml (Zachmann et al., 1974). Basal serum levels of testosterone, LH and FSH were low. Gonadotropin reserves to LH-RH (200 µg, iv) were intermediate. These findings were comparable to those of the prepubertal state.

Therapy for Small Stature

The clinical course of the therapy for small stature is summarized in Fig. 1. At
the age of 8 and 2/12 yrs, he was started on dessicated thyroid medication (40–80 mg/day). Since the age of 9 and 2/12 yrs, when the height was 106.9 (128.8) cm and the bone age was 4 yrs, he has been receiving stanozolol (an anabolic steroid, 1–2 mg/day). At the age of 10 and 2/12 yrs, the height was 114.0 (133.7) cm and the bone age was 6 yrs. When he was 11 and 2/12 yrs, the height was 119.5 (138.8) cm and the bone age was 7 and half yrs. Since then, he has been treated with 6 IU hGH twice a week. At the age of 12 and 2/12 yrs, the height was 130.5 (144.9) cm and the bone age was 9 and half yrs. At the age of 14 and 2/12 yrs, the height was 141.5 (158.4) cm, the bone age was 11 and half yrs and testicular volume was 1.4 ml.

### Table 2. Endocrinological data II (12 years)

<table>
<thead>
<tr>
<th>RIA</th>
<th>minutes</th>
<th>normal (M±SD)</th>
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<tbody>
<tr>
<td>LH (mIU/ml)</td>
<td>4-10</td>
<td>15 16 9±4 53±17</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>4-10</td>
<td>15 16 10±4 19±3</td>
</tr>
</tbody>
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2) Gonadal function

- Testosterone (ng/dl) patient below 25 (90±40)
- Public chair (stage) I (I)
- Genitalia (stage) I (II)
- Testicular volume (ml) 0.8 (5±4)

### Eye Examination

Eye examination was performed at the age of 12 yrs.

The eyes were mobile in all directions. Frequent horizontal roving nystagmus and rare convergent nystagmus were recognized. Direct and indirect pupillary reflex were present in both eyes. Visual acuity of the left eye was light sinn and that of the right eye was normal. Frequent horizontal roving nystagmus and rare convergent nystagmus were recognized. Direct and indirect pupillary reflex were present in both eyes. Visual acuity of the left eye was light sinn and that of the right eye was normal.

Fig. 2. The right fundal photograph; showing mild hypoplasia of disc with temporal conus-like change.

Fig. 3. The left fundal photograph; showing typical hypoplasia of disc with double margin.
Fig. 4. Plain computed tomograph; showing the presence of the septum pellucidum.

Fig. 5. Plain computed tomograph; showing an enlargement of the suprachiasmatic cistern.
eye was 0.3 (0.4–1.5 D). The visual field of the left eye could not be examined and that of right eye showed a slight defect in the upper portion.

The optic disc of the right eye (Fig. 2) was almost normal in size, slightly white in colour and had a conus-like change in the auricular position. That of the left eye (Fig. 3) was small in size, white in colour and surrounded by a white-yellow area. In both eyes, the retinal colour was somewhat white and the optic nerves were identifiable. The retinal vessels were normal.

**Computed Tomograph (CT)**

Plain CT showed that the septum pellucidum was present (Fig. 4) but the suprachiasmatic cistern was large (Fig. 5). The cerebral sulci were normal.

**Discussion**

This syndrome is a clinical entity which includes; hypoplasia of the optic nerves, chiasma and the optic tracts; lack of the septum pellucidum and/or primitive optic ventricle; pituitary hypofunction.

In the syndrome, examination of the fundus showed a small disc surrounded by a double margin which was diagnostic in optic hypoplasia. Amblyopia, an irregular defect of the visual field, and nystagmus were usually recognized in affected eyes. Approximately half of the patients with optic hypoplasia were bilateral and the other half were unilateral (Brook et al., 1972; Patel et al., 1975). In my patient the characteristic findings of the disc were seen in the left eye (Fig. 3), and atypical abnormalities were also seen in the left eye (Fig. 2). These findings helped the diagnosis of bilateral optic hypoplasia to be made in this case. Roving nystagmus in the case might indicate a hypothalamic origin.

In the past, a pneumoencephalogram confirmed structural abnormalities of the brain. The septum pellucidum was absent in 3 out of 4 patients examined by Kaplan et al. (1970), in 1 out of 2 patients examined by Billson and Hopkins (1972), and in 2 out of 3 patients examined by Patel et al. (1975). The suprachiasmatic cistern was found dilated in 3 out of 4 patients examined by Kaplan et al. (1970), in all 4 patients examined by Brook et al. (1972) and in all 3 patients examined by Patel et al. (1975). Some reports (Kaplan et al., 1970; Brook et al., 1972; Harris and Haas, 1972; Patel et al., 1975) referred to rather rare findings, such as abnormal fornices, irregular lamina terminalis, abnormally shaped 3rd ventricle and enlarged lateral ventricle.

In the present study, CT confirmed an enlargement of the suprachiasmatic cistern (Fig. 5) and the presence of the septum pellucidum (Fig. 4). Today, it may be advisable that children with blindness, or near blindness, and growth retardation undergo CT scanning which involves no hazard.

There was no hereditary tendency, but the patients were usually the first born children of young mothers. Ellenberger and Runyan (1970) explained the hypothesis that the syndrome resulted from the failure of the mesoderm in the early stage of growth. At 4 mm stage (5 weeks), the optic vesicles and the telencephalic vesicles begin to expand from the wall of the prosencephalon. At the 15 mm stage (6 weeks), a thickening (lamina reuniens) begins to develop in the dorsal part of the anterior wall of the neural tube (lamina terminalis). Within the lamina reuniens, the forebrain commissures and eventually the septum pellucidum form. The first appearance of the septum pellucidum at 145 mm (18 weeks) depends on the above and many other complex preceding events. When these processes are disturbed, development of the prosencephalon may be arrested.

In the syndrome, Kaplan et al. reported
that out of 6 patients, the 6 patients had GH deficiency, the 4 patients multiple tropic hormone deficiency and the 2 patients ADH deficiency. Brook et al. (1972) said in their report that out of 3 patients, two had isolated GH deficiency and the other patient had evidence of panhypopituitarism. Patel et al. (1975) showed that all 3 patients examined had GH deficiency, 2 out of 3 patient examined had low thyroidal radioactive iodine uptake and abnormal water deprivation test, and 2 out of 4 patients examined had diminished Metopirone response. Only 3 patients in the past had reached pubertal age. Ellenberger and Runyan (1970) showed a woman with normal puberty. Huseman et al. (1978) described the 2 other females who showed sexual precocity. Although precocious puberty often occurs in association with hypothalamic lesions, it rarely occurs along with pituitary hypofunction.

I diagnosed the case as pituitary dwarfism because of the complete lack of GH responses to various provocation tests (Table 1), in addition to the clinical findings of dwarfism, infantilism and delayed bone maturation. Diminished Metopirone response (Table 1) suggested the latent deficiency of ACTH secretion. Intermediate responses of LH and FSH may account for the delay in pubertal development (Table 2). Delayed TSH response to TRH, and poor or subnormal response of 17 OHCS, LH, FSH and PRL to each provocation tests indicate an hypothalamic origin of secondary anterior hypopituitarism.

With regard to somatic growth, the patient has been treated with several combinations of thyroid, anabolic steroid and hGH (Fig. 1). The first year of therapy with thyroid alone resulted in a 5.3 cm/yr height increase and 0.6 growth index (height age increase/bone age increase), the first year of the therapy with thyroid and anabolic steroid 7.1 cm/yr and 0.7, the first year of the present therapy with thyroid, anabolic steroid and hGH 11.0 cm/yr and 1.1, respectively. At the age of 14 and 2/12 yrs, his height (141.5 cm-height age 11 and 8/12 yrs) was still small for his chronological age, but his bone age was 11 and half yrs and there were no secondary sex characteristics. He is expected to attain normal height ultimately when the present therapy can be continued.

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