The syndrome of septo-optic dysplasia in Saudi children

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ABSTRACT

Objective: To describe the clinical, ophthalmological, endocrinological and radiological features of 10 Saudi children with the syndrome of septo-optic dysplasia and hypothalamic hypopituitarism

Methods: All patients underwent complete ophthalmological and endocrinological evaluation at the Pediatric Endocrine Clinics, King Faisal Specialist Hospital and Research Center and King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia, from October 1999 through to May 2004. The hormonal evaluation included growth hormone, adrenocorticotrophic hormone, thyroid stimulating hormone, gonadotropin and anti diuretic hormone testing, and the neuroradiological assessment included brain magnetic resonance imaging or computed tomogram scanning, or both.

Results: The current age of patients ranged from 18-months to 5-years. The mean age of initial presentation for endocrine evaluation was 14-months. Hormonal studies indicated that all children had multiple pituitary hormone deficiencies (2 or more of the pituitary hormones were deficient). Ten children had growth hormone deficiency, 8 had thyroid stimulating hormone deficiency, 8 had adrenocorticotrophic hormone deficiency, 2 children were suspected to have gonadotropin deficiency and central diabetes insipidus was present in one patient. Pendular nystagmus and impaired vision were common initial signs. All children had bilateral optic nerve hypoplasia. Neuroradiologic findings were variable. Eight children had absent septum pellucidum, 3 had pituitary gland hypoplasia, 2 had pituitary stalk dysplasia (pituitary stalk was either attenuated or not visualized), 2 had absent corpus callosum and one had absent posterior pituitary high intensity signal. All patients were replaced with appropriate hormonal replacement therapy. Two male children had micropenis which responded to testosterone therapy.

Conclusion: The syndrome of septo-optic dysplasia is commonly associated with hypothalamic hypopituitarism including anterior and posterior pituitary hormonal deficiencies. Early diagnosis of this syndrome is critical as the hormonal deficiencies can be life threatening.

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The syndrome of septo-optic dysplasia is a congenital malformation variable in severity that involves forebrain midline structures including the septum pellucidum, the optic system and the hypothalamic-pituitary axis. A connection between optic nerve hypoplasia and septum pellucidum agenesis was noted by Reeves.[1] In 1956 de Morsier[2] described the neuropathology of this developmental malformation of the prosencephalon including absent septum pellucidum, a primitive optic vesicle and hypoplasia of optic nerves. The association of congenital anterior or posterior hypopituitarism with septo-optic dysplasia, or both was first recognized in 1970.[3,4] Subsequent reports have confirmed the

characteristic features and the variable phenotypic expression of this syndrome including incomplete forms. In this report, we describe the clinical, hormonal and radiological features of septo-optic dysplasia in 10 Saudi children who were followed at the Pediatric Endocrine Clinics, King Faisal Specialist Hospital and Research Center and King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia.

Methods. The clinical and hormonal features of 10 patients (6 males, 4 females) with sporadic optic nerve hypoplasia associated with hypothalamic-hypopituitarism and midline brain defects are described. The diagnosis of optic nerve hypoplasia or dysplasia was based on the presence of some or all of the following features: 1. Small size of the optic nerve head; 2. The double pigmentary ring sign of the optic nerve 3. Abnormal nerve fiber layers and 4. Tilting of the optic nerve head 5. Hypothalamic-pituitary function was evaluated at the time of presentation. Pituitary hormone deficiencies were documented using standard tests and radioimmunoassays. Growth hormone (GH) was measured in response to insulin-induced-hypoglycemia and clonidine stimulation tests. Adrenocorticotrophic hormone (ACTH) reserve was assessed by the rise in plasma cortisol evoked by insulin-induced-hypoglycemia, or ACTH stimulation test, or both. Thyroid stimulating hormone (TSH) reserve was evaluated by measuring plasma free T4 and TSH. Gonadotropin reserve was assessed by measuring follicular stimulating hormone (FSH) and leuteinizing hormone (LH). Posterior pituitary function was ascertained by the water deprivation test, random concurrent urine/serum osmolality determinations, monitoring fluid input and output records, and by determination of the concentration of plasma arginine vasopressin at the end of a water deprivation test. The patients were evaluated by brain computed tomogram (CT) scan or magnetic resonance imaging (MRI) with contrast, or both. The imaging studies included views to identify midline brain defects and the appearance of the hypothalamus, the pituitary gland and the optic nerves.

Results. The birth weights of these children ranged from 3.1-4 kg (mean 3.4 kg). The birth lengths ranged from 49-52 cm (mean 51cm). The mean age at the time of initial presentation for evaluation of pituitary endocrine function was 14-months (range: birth to 5-years). Pendular nystagmus and impaired vision were common initial findings. All children had bilateral optic nerve hypoplasia and 7 of them were legally blind. All children were short (their heights ranged from -4 SD

to -2.5 SD below the mean value for age; mean -3.3 SD). Two male children presented with micropenis at birth and were treated with testosterone. Hypoglycemia was documented in 3 patients. One of them had hypoglycemic seizure. There was no recurrence of convulsive episodes once he became euglycemic on hormonal replacement therapy. The neonatal course of one patient was associated with cholestatic jaundice. This child had ACTH, GH, and TSH deficiency. The jaundice resolved after replacement hormonal therapy. Delayed cognitive and psychosocial development was present in 4 patients. These patients had severe central nervous system abnormalities and had delayed recognition of chronic hypoglycemia and severe fluid and electrolyte imbalance. Four patients were offspring of young mothers (maternal age <20-year-old). Six patients were the first-born children. Four children were products of full term pregnancies and consanguineous parents. Two mothers had gestational diabetes mellitus. No history of familial cases. All children had multiple pituitary hormone deficiencies (2 or more pituitary hormones were affected). Ten children had GH deficiency as a part of multiple pituitary hormone deficiencies and 2 of them had isolated GH deficiency. The peak GH response to provocative stimuli ranged from 2-12 IU/l. Growth hormone deficient children responded to hGH treatment with an increase in their growth velocity. Eight children had TSH deficiency and started oL-thyroxine replacement therapy which kept them euthyroid. Eight children had ACTH deficiency and replaced with 10-15 mg/m2/day of hydrocortisone. Two male children were suspected to have gonadotropin deficiency based biochemical evidence of low gonadotropins (FSH 2 IU/l, LH <2 IU/l) and clinical observation of micropenis (stretched penile length <2.5SD for age). They were treated with a one to two, 3 monthly courses of intramuscular testosterone enanthate with a good response (stretched penile length improve to -1.5 SD). Central diabetes insipidus was present in one child with an impaired thirst mechanism. On neuroradiologic studies, 8 children had absent septum pellucidum, 2 had pituitary stalk dysplasia (pituitary stalk was either attenuated or not visualized), 3 had pituitary gland hypoplasia and 2 had absent corpus callosum. The child with diabetes insipidus had an absent posterior pituitary high intensity signal.

Discussion. Septo-optic dysplasia patients present with a variable constellation of symptoms and signs depending on the degree of hypothalamic-pituitary-optic nerve and central nervous system impairment. Ophthalmologic symptoms usually predominate and the diversity of ophthalmological findings depends on the severity

of the optic nerve hypoplasia. In our series, all children had bilateral optic nerve hypoplasia and 7 of them were legally blind. The impairment of vision may range from complete blindness to subtle impairment. Pendular nystagmus was the most frequent presenting sign and optic nerve hypoplasia the most common associated neurological anomaly. Optic nerve hypoplasia is usually bilateral, but it can be asymmetrical in appearance or unilateral.[5-7] In a review of 93 children with optic nerve hypoplasia the ophthalmological findings were related to the severity of central nervous system abnormality, the degree of developmental delay and the prevalence of hormonal deficiencies.[5] Septum pellucidum agenesis occurred in 8 children emphasizing that absence of the septum pellucidum is not a constant finding in the syndrome of septo-optic dysplasia. The pituitary stalk was attenuated or not visualized in 2 patients who had a brain MRI. Failure to visualize the pituitary stalk has been described in patients with this syndrome.[8] Neurological symptoms variable[9-14] and are related to the extent of the anatomical brain malformation and the neonatal history of prolonged or recurrent hypoglycemia, hypernatremia and dehydration. The spectrum of endocrinological abnormalities secondary to the congenital hypothalamic-pituitary dysfunction associated with septo-optic dysplasia is variable.[9,11,12,14] Growth hormone was the most common pituitary hormone deficiency followed by TSH, ACTH, and less commonly anti diuretic hormone (ADH). Multiple pituitary hormonal deficiencies occurred more commonly with bilateral optic nerve hypoplasia. Hellstrom et al[15] reported that 3 children with multiple pituitary hormonal deficiencies and optic nerve hypoplasia had a lower GH response to provocative tests than patients with isolated GH deficiency. Hypopituitarism in septo-optic dysplasia may be severe at birth and involve both anterior and posterior pituitary hormones, or the hormone deficiencies may evolve with advancing age. One patient in our series had a pattern of the progressive onset of multiple pituitary hormonal deficiencies over several years. This suggests that in patients with optic nerve hypoplasia a thorough endocrinological assessment is indicated initially, followed by regular evaluations to detect an evolving hormonal deficiency which may be subtle and subclinical. Children with septo-optic dysplasia associated with hypocortisolism, diabetes insipidus and temperature instability may die suddenly and unexpectedly during an intercurrent febrile illness. Brodsky et al[16] reported the occurrence of sudden death in 5 patients with septo-optic dysplasia during febrile illnesses secondary to thermoregulatory disturbances, hypoglycemia, dehydration or hypocortisolism. Close endocrinological monitoring and special precautionary measures (ensure adequate hydration, protect against hypoglycemia, and increase the dose of glucocorticoid during intercurrent illnesses) are essential to minimize the risk of sudden death in septo-optic dysplasia patients with multiple pituitary hormone deficiencies. The syndrome of septo-optic dysplasia is a heterogeneous disorder and most commonly quite likely a multifactorial disorder. Familial cases are rare.[17-19] The weight of evidence suggests the causes are mainly a consequence of the complex interaction of genetic and environmental factors. Homozygous and heterozygous mutations in HESX1 gene were reported in patients with septo-optic dysplasia.[20,21] Mice lacking Hesx1 exhibit pituitary hypoplasia and central nervous system abnormalities including defects in the septum pellucidum, the corpus callosum, the anterior and hippocampal commissures and eye anomalies.[22] The occurrence of septo-optic dysplasia was described in one member of a family with Waardenburg syndrome (WS), an autosomal dominant disorder characterized by facial pigmentation and deafness. A G to C transversion was identified in exon 7 of PAX3 gene in the 4 family members affected with WS type I including the patient with SOD.[23] Mice deficient in Netrin-1 or its receptor genes have optic nerve dysplasia, absent corpus callosum, and die soon after birth.[24] All these genetic factors were suspected to be candidate genes for the syndrome of septo-optic dysplasia. In holoprosencephaly (HPE), the most common structural anomaly of the embryonic forebrain and a central nervous system malformation which shares certain phenotypic characteristics with the syndrome of septo-optic dysplasia, 2 different heterozygous mutations (SHH [sonic hedgehog][25] and ZIC2[26] have been described in autosomal dominant holoprosencephaly. And in relation to the action of SHH, HPE can occur in the Smith-Lemi-Optiz syndrome due to mutations in the gene (DHCR7) encoding D7-dehydrocholestrol reductase.[27] It is suggested that loci involved in HPE reside on 11 different chromosomes.[28] The major risk factor in the pathogenesis of septo-optic dysplasia young maternal age[9,11,29,30] is well established and it is associated with a high prevalence in first born offspring. In our series, 4 children were offsprings of young mothers and 6 patients were the first born children. Additional risk factors such as gestational diabetes mellitus, substance abuse, teratogens, intrauterine infection, vascular disruption event in the embryonic brain and other unknown environmental factors are suspected either to play an independent role in the pathogenesis of septo-optic dysplasia or to interact with susceptibility genes for the anomaly.[9,15,29-33] It is clear that large gaps remain in our understanding of the cause(s) of septo-optic dysplasia.

In conclusion, the syndrome of septo-optic dysplasia is commonly associated with hypothalamic hypopituitarism including anterior and posterior pituitary hormonal deficiencies. Early diagnosis of the syndrome of septo-optic dysplasia is critical as the hormonal deficiencies can be life threatening. Hypoglycemia, neonatal cholestatic jaundice, pendular nystagmus, polyuria, micropenis and optic nerve hypoplasia suggest the diagnosis.

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