

REVIEWS & COMMENTS FROM THE LITERATURE

Childhood Hypopituitarism after Traumatic Brain Injury

The hypothalamus and pituitary are essential for childhood and adolescent development and are vulnerable to injury and dysfunction following brain trauma. Hypothalamic-pituitary dysfunction has been well recognized after traumatic brain injury (TBI) in adults. However, data regarding hypothalamic-pituitary function in brain-injured children and adolescents are scant. It is necessary for physicians as well as patients and family members to know that onset of hypothalamic-pituitary deficits can occur even after several years following brain injury.

Acerini et al reviewed the available pediatric data, which showed that after both mild and severe TBI, hypopituitarism may occur; growth hormone (GH) and gonadotropin deficiencies appear to be most common. Precocious puberty has also been documented. Detailed investigations of pituitary function have been reported in 20 patients (12 males, 7 females, and 1 sex unspecified). Subjects ranged in age from infancy to 16 years at the time of injury; they were investigated between 1 and 42 years after the initial episodes of TBI. All patients had multiple anterior pituitary hormone deficiencies, except one, who had isolated GH deficiency. The frequencies of deficient hormones were: GH 85%, LH/FSH 80%, TSH 75%, and ACTH 50%. It was notable that in 6 patients, multiple deficiencies were documented after relatively mild head injury without loss of consciousness. Pituitary stalk transection was demonstrated on MRI in several cases. The diagnosis of hypothalamic-pituitary deficiency was made during childhood and adolescence in 17 of the 20 patients and during adult life in the remaining 3. The key presenting symptoms were growth failure, delayed or arrested puberty, secondary amenorrhea or reduced libido. Delay in the diagnosis was extreme in many cases and hypopituitarism was clearly not considered as a possible complication of the TBI until defects of growth or reproductive function became obvious.

Acerini and colleagues urged pediatric endocrinologists, in collaboration with adult endocrinologists, to perform formal prospective research studies in patients suffering from TBI to clarify prevalence, natural history, and response to hormone replacement.

Acerini CL, Tasker RC, Bellone S, Bona G, Thompson CJ, Savage MO. Hypopituitarism in childhood and adolescence following traumatic brain injury: the case for prospective endocrine investigation. *Eur J Endocrinol.* 2006;155:663-9.

First Editor's Comment: *This is a very interesting report which provides important information for physicians who care for patients with TBI. Traumatic brain injury is a worldwide health problem and a major leading cause of death and disability among young adults. Survivors are*

often left with significant neuroendocrine dysfunction and adverse physical and/or psychological problems which are perhaps an even greater risk than previously considered. As well, TBI-induced hypopituitarism has been under-recognized, under-investigated, and untreated. Relatively little attention has been paid to the possibility of TBI-induced hypopituitarism, especially in children. As reported by Acerini et al, it became clear that TBI posed substantial risk to hypothalamic-pituitary function in children; the onset of hypopituitarism can evolve over years following injury.

Road-traffic accidents, falls, sports injuries, and child abuse are the most common etiological factors for pediatric TBI, although the causes are different among age groups. The perinatal brain injury such as difficult forceps delivery at breech delivery is a well-known cause of hypopituitarism. Infants with TBI have primarily suffered from falls or assaults. Toddlers are more frequently injured as passengers in motor vehicle accidents, although falls still account for the majority of injuries. Children and infants have large, heavy heads with weaker cervical ligaments and muscles compared to adults. Given the same deceleration of the body, head trauma is therefore more likely in infants and younger children than adults. Similarly, the resulting brain injury may be more severe due to the thin, pliable skull and unfused sutures of infants and young children. Possible causes of hypopituitarism include hemorrhage, infarction, ischemia, swelling, stalk transection, or direct trauma to the hypothalamus, stalk, and/or pituitary region. Severity of TBI seems to be an important risk factor for developing hypopituitarism; however, even mild trauma may precede hypopituitarism. Accurate evaluation and long-term follow-up of all TBI patients are necessary in order to detect the occurrence of hypopituitarism, regardless of clinical evidence for pituitary dysfunction. The most common endocrine alterations appear to be GH and gonadotropin, followed by ACTH and TSH deficiency. Hyperprolactinemia may also be present. Diabetes insipidus may be frequent in the early, acute phase post-TBI, but it is rarely permanent.

The signs and symptoms of TBI-induced hypopituitarism are often nonspecific and can be additionally masked by what has been assumed to be merely the post-traumatic syndrome. These symptoms are likely to be overlooked if endocrine dysfunction is not actively evaluated. Moreover, hormonal deficits may significantly contribute to the chronic disability and the physical, cognitive, health, and social sequel in patients with TBI. Therefore, regular endocrine evaluation and follow-up should be performed throughout life in patients with TBI. In most instances, patients with

TBI are first seen and treated by trauma surgeons and neurosurgeons, and subsequently by rehabilitation specialists; all physicians must be informed about the risks of TBI-induced hypopituitarism. It is important to increase awareness among physicians, patients, and family members of the risks of hypopituitarism and the need for appropriate endocrinological assessment and adequate hormonal replacement therapy, if necessary. Thorough assessment may make it possible to improve the quality of life and enhance the rehabilitation prospects. Lack of awareness of this problem may result in long-term adverse consequences of untreated hypopituitarism for these patients. A close collaboration among neurosurgeons, neurologists, rehabilitation specialists, and endocrinologists is essential to achieve a coordinated approach to the care of patients with TBI.

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Second Editor's Comment: *The consensus guidelines on screening for hypopituitarism following TBI for adults¹ was published in 2005. These guidelines may also apply to children and adolescents as the data in the paper by Acerni et al on the development of hypopituitarism following TBI are similar to the reported alterations found in adults. A summary of selected studies was presented in a tabular form in the consensus statement. However, the appropriate diagnosis and treatment of the endocrine alterations should always be accompanied by evidence-based cognitive rehabilitation of those patients; these recommendations for clinical practice were published by Cicerone et al.²*

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References

1. Ghigo E, Masel B, Aimaretti G, et al. Brain Inj. 2005;19:711-24.
2. Cicerone KD, Dahlberg C, Kalmar K, et al. Arch Phys Med Rehabil. 2000;81:1596-615.

The Value of Clinical and Radiological Expertise in Mutation Screening

As with many types of genetic disease, it is becoming common for clinical diagnosis of skeletal dysplasias to be confirmed at the DNA level. An issue that often arises is whether or not cases submitted for DNA diagnosis should be evaluated by experts before performing DNA testing. A small study involving multiple epiphyseal dysplasia (MED) reported by Zankl et al suggests that preselection of cases through such evaluation significantly increases the rate of mutation detection. The investigation was carried out under the auspices of the European Skeletal Dysplasia Network (ESDN).

MED is characterized by delayed and irregular ossification of epiphyses and precocious osteoarthritis. It is inherited as a dominant trait in most cases, and mutations have been identified in genes encoding 5 cartilage extracellular matrix proteins including cartilage oligomeric matrix protein (*COMP*), the 3 chains of type IX collagen (*COL9A1*, *COL9A2*, *COL9A3*), and matrilin 3 (*MATN3*). Mutations of *COMP* are most common. MED is occasionally inherited in a recessive fashion with mutations identified in the gene coding for the diastrophic dysplasia sulfate transporter (*DTDST*, *SLC26A2*).

The authors first noted that in a recent study *COMP* mutations were detected in only 36% of 58 families with MED in whom the diagnosis was made by the referring physician, usually a clinical geneticist. Since they expected the rate to be higher they suspected that some of the referral diagnoses were incorrect and that the mutation detection rate could be improved by adding an expert evaluation step between referral and DNA diagnosis.

Between September 2003 and February 2005 a panel of experts in the clinical and radiographical aspects of skeletal dysplasias evaluated, before testing, 35 patients with a diagnosis of MED. Of the 35 patients,

24 were considered to have "classical" MED by the experts, 5 possible MED variants, 2 most likely had type II collagenopathy, and 4 patients were considered "unknowns." Genomic DNA was analyzed from 21 of the 29 patients with classical or possible variant MED. Mutations were detected in 13 of the 16 patients with classical MED and one with a possible MED variant. Of the 14 mutations identified, 13 were *COMP* mutations and one involved *MATN3*. A *COL2A1* mutation was subsequently identified in the patient with clinical features of type II collagenopathy. No mutation was detected in 3 patients considered to have classical MED.

When the numbers were tallied, the mutation detection rate was 81% for patients with classical MED and 67% if patients with possible MED variant were included, both substantially higher than the 36% reported previously. The authors concluded that review of clinical and radiographical features by experts prior to DNA testing substantially improves the rate of mutation detection since cases misdiagnosed by non-experts are excluded. The results also confirm that mutations of *COMP* are responsible for most cases of MED.

Zankl A, Jackson GC, Crettol LM, et al. Preselection of cases through expert clinical and radiological review significantly increases mutation detection rate in multiple epiphyseal dysplasia. Eur J Hum Genet. 2007;15:150-4.

Editor's Comment: *From time to time the skeletal dysplasia community debates the value of clinical and especially radiographical expertise in the diagnosis of skeletal dysplasias. The argument is sometimes made that with DNA diagnosis becoming easily accessible through academic and commercial laboratories and government-sponsored networks such as the ESDN, there is no longer a need for special expertise in*