Precocious puberty following head injury

Case report

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A 6-year-old girl developed secondary sexual characteristics 5 months after severe closed head injury.
Endocrinological tests confirmed a pubertal sexual condition; there was also diminution of serum melatonin
and disruption of the diurnal pattern. Magnetic resonance imaging demonstrated focal hypothalamic injury;
this is believed to be the first time such a posttraumatic lesion has been demonstrated by imaging techniques.
The pathophysiology of this condition is discussed.

KEY WORDS • gonadotrophin • precocious puberty • head injury • hypothalamus

SEXUAL precocity may be defined as the onset of secondary sexual characteristics before the age of
8 years in girls or 9 years in boys. It may be the result of hypothalamic involvement by tumor or infec-
tion, but it is an exceedingly rare sequela of head injury. Only four case reports establishing a causal relationship
between trauma and sexual precocity have been published in the last two decades.22,29,30 Reproductive func-
tion, manifested by the secretion of gonadotrophins and gonadal steroids, is active during fetal life but
regresses during early infancy and remains quiescent until toward the end of the first decade of life. Recent
studies suggest that sexual maturation at puberty is triggered by an increase in the pulsatile frequency of
gonadotrophin-releasing hormone (GnRH), a decapetide secreted by the arcuate nucleus of the medial basal
hypothalamus.20,38 Pituitary gonadotrophin secretion is regulated by gonadal steroids which act partly by mod-
ulating the amplitude and frequency of GnRH; they probably alter the levels of endogenous hypothalamic
neurotransmitters to influence this pulsatile secretion.

Hypothalamic catecholamines stimulate,14 while endogenous opioid peptides (endorphins and enkephalins)
inhibit, GnRH pulse frequency.24,33,34 Prior to puberty, the reproductive system appears to be under the re-
straint of the central nervous system (CNS), although the nature and locus of this inhibitory influence re-
 mains to be defined. Much circumstantial evidence has accumulated to implicate the pineal gland in the regu-
lation of puberty through the secretion of its antigo-

Case Report

This 6-year-old girl was struck by a car while crossing a road and was admitted to a local hospital in a com-
atoe condition with fixed and dilated pupils. She was breathing spontaneously and no periods of hypoxia or
hypotension were noted. Following the placement of an endotracheal tube, intravenous Dilantin (phenytoin)
was administered and she was transferred to the Children's Hospital in Boston within 3 hours of injury.

Examination. On admission, the patient was co-
matose and demonstrated decerebrate posturing in re-
response to painful stimuli. There were bilateral hemo-
tympani and blood dripping from both nares. The
pupils were 6 mm bilaterally and fixed. Funduscopic
examination revealed bilateral retinal hemorrhages, no
spontaneous venous pulsations, and early disc edema.
Corneal and oculocephalic reflexes were absent. There
was a minimal gag reflex. Deep-tendon reflexes on both
sides were hyperreflexic. Babinski reflexes were present
bilaterally. The cervical spine films were normal. There
was no major injury to any other organ system.
Computerized tomography (CT) disclosed a basilar skull fracture involving both petrous pyramids, the frontal sinuses, and the sellar region. The scan also revealed a hemorrhagic contusion of the right posterior temporal region over the petrous bone with deep extension into the subthalamus, together with a hyperdense area along the tentorium consistent with a subdural tentorial hematoma (Fig. 1). A high-density lesion in the pons, midbrain, and above the quadrigeminal plate cistern (which was obscured) was consistent with an intraparenchymal hemorrhage up to the level of the tegmentum, posterior commissure, and mamillary body. Intraventricular hemorrhage was noted manifested by blood in the posterior horns of the lateral ventricles. Diffuse cerebral edema was identified, and there were small lateral ventricles without a midline shift, a small midline fourth ventricle, and absent basilar cisterns. Pneumocephalus was noted in the frontal, orbital, and suprachiasmatic regions.

**Hospital Course.** The patient was given intravenous mannitol and Decadron (dexamethasone). An arterial line and Foley catheter were placed, and she underwent controlled hyperventilation to maintain her PaCO₂ between 25 and 30 mm Hg. A right frontal pediatric subarachnoid bolt was inserted for intracranial pressure (ICP) monitoring; the initial ICP measured 15 to 17 mm Hg. For the next 72 hours, she received maximum medical treatment, consisting of elevation of her head, fluid restriction with maintenance of adequate intravascular volume, mannitol/呋塞米 boluses, fentanyl for sedation, prophylactic oxacillin while the bolt was in place, and pancuronium for neuromuscular block-

![Fig. 1.](image)

The patient was weaned off the ventilator after the 1st week of hospitalization, and enteral alimentation by nasogastric tube was begun. Generalized tonic-clonic motor seizures secondary to hyponatremia were treated with anticonvulsant drugs, and the hyponatremia was managed with 5% intravenous saline and fluid restriction. Investigation of persistent pyrexia revealed lobar pneumonia and opacified maxillary sinuses. A transnasal maxillary sinus puncture with aspiration was performed 12 days postinjury and intravenous penicillin, mezlocillin, and gentamicin were subsequently given. Cerebrospinal fluid obtained from two lumbar punctures was sterile. The patient's fever defervesced due to the antibiotics. Thirteen days after injury her endotracheal tube was removed, and her neurological condition gradually improved. She began to follow simple commands by lifting her head off her pillow, opening her mouth, and moving her spastic extremities spontaneously. Her pupils remained fixed and dilated. She was transferred to a rehabilitation hospital on the 37th day after injury in stable but improved neurological condition. Six weeks after admission, she began to respond to verbal commands. A CT scan revealed hydrocephalus and diffusely enlarged ventricles and sulci.

### TABLE 1

**Results of endocrinological testing**

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Patient Data</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>chronological age at testing</td>
<td>7 yrs</td>
<td></td>
</tr>
<tr>
<td>bone age</td>
<td>8 yrs 10 mos</td>
<td></td>
</tr>
<tr>
<td>serum cortisol (µg/dl)</td>
<td>12.9</td>
<td>5–25</td>
</tr>
<tr>
<td>serum thyroxine (µg/dl)</td>
<td>6.8</td>
<td>4–12</td>
</tr>
<tr>
<td>serum T₃ (ng/ml)</td>
<td>226.0</td>
<td>75–195</td>
</tr>
<tr>
<td>serum TSH (µU/ml)</td>
<td>2.8</td>
<td>0.5–5.0</td>
</tr>
<tr>
<td>serum prolactin (ng/ml)</td>
<td>13.9</td>
<td>0.15</td>
</tr>
<tr>
<td>serum somatotropin-C</td>
<td>2.9</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>(IU/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum DHEA-S (ng/ml)</td>
<td>10.0</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

* T₃ = triiodothyronine; TSH = thyroid-stimulating hormone; DHEA-S = dehydro-3-epiandrosterone.

### TABLE 2

**Gonadotrophin-releasing hormone (GnRH) test***

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>FSH (mIU/ml)</th>
<th>LH (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13.2</td>
<td>7.7</td>
</tr>
<tr>
<td>60</td>
<td>16.5</td>
<td>43.3</td>
</tr>
</tbody>
</table>

* FSH = Follicle-stimulating hormone; LH = luteinizing hormone. Normal basal concentrations of LH and FSH in prepubertal children are <8 mIU/ml and <3 mIU/ml, respectively. Typical responses of children to GnRH stimulation are as follows (mean ± standard deviation in mIU/ml): for prepubertal children, the LH increment is 7.1 ± 3.4 and FSH increment is 7.6 ± 10.0; for pubertal children, the LH increment is 42.0 ± 14.5, and the FSH increment is 6.6 ± 4.1.
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Rehabilitative Course. Five months after the accident, when the patient was aged 6 years 8 months, breast development and pubic hair growth were noted. At the age of 7 years, she underwent a full endocrinological evaluation. She had both axillary and pubic hair. Breast development was found to be consistent with Tanner stage IV, and her vaginal mucosa was well estrogenized. Bone age was assessed, together with determinations of serum cortisol, thyroxine, triiodothyronine, thyroid-stimulating hormone, prolactin, somatotropin-C, and dehydro-3-epiandrosterone levels (Table 1). The somatotropin-C level, which rises significantly with the increase in sex steroid levels, was elevated. This effect of sex steroids on somatotropin-C levels during puberty may be mediated through growth hormone stimulation.11

The patient's bone age was found to be 8 years 10 months. The remaining indices were within normal limits, indicating normal pituitary function and the absence of adrenarche. A GnRH stimulation test elicited a pubertal rise in both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels (Table 2). Prior to injury, her growth and development had been normal.

Twenty-seven months after injury, the patient had markedly improved both physically and neurologically. She was 8 years 3 months old and in the second grade: approximately 1 year delayed. Her speech was fluent and grammatical. However, her prosody was reduced and her speech tended to be hypophonic. She demonstrated significant word-finding difficulties and deficits in auditory verbal memory and execution of visual motor tasks; regardless of this, neuropsychological testing revealed a good overall recovery, particularly in the areas of reasoning, judgment, and abstraction.

Funduscopic examination revealed optic pallor consistent with early atrophy. There was no papilledema. She had weakness of the third, fourth, and sixth cranial nerves, with bilateral ptosis. She showed no facial asymmetry and her deep-tendon reflexes remained symmetrically hyperactive. A left hemiparesis, evident during her initial rehabilitation, was now negligible. Results of gait, cerebellar, and sensory testing were normal.

Radiological Investigations. Twelve months after the accident, magnetic resonance (MR) imaging in the sagittal and the coronal projections was performed (Fig. 2). The sagittal MR image clearly showed two pinpoint brain-stem lesions, one in the region of the mammillary bodies and the second in the tegmentum. The coronal MR image revealed diffuse unilateral right-sided atrophy of the posterior hypothalamus.

Laboratory Investigations. Twelve months after the patient's accident, her serum melatonin levels were determined over a 24-hour period as described below and elsewhere.35 The informed consent of the parents was obtained for blood collection. The patient experi-

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Fig. 2. Magnetic resonance images. *Left:* Sagittal projection depicting focal hypothalamic damage (arrows), one in the region of the mammillary bodies (MB) and the second in the tegmentum (T). Enlarged view is shown (lower center). *Right:* Coronal projection revealing right-sided atrophy of the mid hypothalamus (arrows). Enlarged view is shown (upper center).
enced normal indoor white light from the onset of darkness until 2200 hours. Blood was collected at night by dim fluorescent light; the patient was only minimally disturbed because an indwelling intravenous needle had been inserted and kept open by 0.9% saline infusion. Blood specimens (2 ml) for determination of serum melatonin levels were collected at 2-hour intervals over the 24-hour period.

Due to the difficulty in obtaining control circadian melatonin data from normal prepubertal children, previously published control data are reproduced with permission from the authors, who used an identical melatonin assay. Figure 3 shows the mean circadian plasma melatonin levels in five regularly ovulating women and the 24-hour profile of plasma melatonin integrated concentrations in 10 peripubertal boys. This second study employed a different melatonin assay, which yielded results within the same range (20 to 120 pg/ml). Our patient displayed lower values than the adult controls, together with a loss of circadian rhythmicity (Fig. 3).

Melatonin concentrations were measured in duplicate 1-ml samples of serum by radioimmunoassay using a specific melatonin antisera. One milliliter serum samples were extracted into 5 ml chloroform: the chloroform extract was then evaporated to dryness under a stream of nitrogen, and the residue was redissolved in 0.5 ml of phosphate buffer (pH 7.5) containing 0.1% gelatin and washed with 1 ml petroleum ether. The buffered extracts of serum samples and buffer samples containing graded concentrations of authentic melatonin were then combined with 100 μl antisera solution (diluted to 1:6000) and 100 μl (3000 cpm) of tritiated melatonin. After the mixture was incubated for 1 hour at 37°C, 0.7 ml of saturated ammonium sulfate was added; the mixture was then incubated overnight at 4°C, and antibody-bound tritiated melatonin was collected as a precipitate by centrifugation. Radioactivity was then measured in a liquid scintillation counter, and melatonin concentrations were estimated by means of the logit-log plot. When 50 or 100 pg/ml of authentic melatonin was added to samples of pooled serum, recovery in the range of 96% to 100% was obtained. The intrasummary coefficients of variation were 8.1% and 10%, respectively. The corresponding interassay coefficients of variation were 17.3% and 7.3%. The sensitivity of the assay (defined as twice the standard deviation of maximum binding) was 5 pg/ml (22 pmol/liter).

Discussion

In this patient, the development of secondary sexual characteristics at the age of 6 years 8 months, together with radiological evidence of focal hypothalamic damage sustained at injury and endocrinological corroboration of a pubertal sexual state, point toward a diagnosis of posttraumatic precocious puberty. The underlying events in the initiation of puberty include premature activation of the hypothalamo-pituitary axis, manifested by an increase in pulsatile frequency and amplitude of GnRH, an enhanced sensitivity of pituitary gonadotrophs to this stimulation, and a decreased responsiveness of the hypothalamo-pituitary axis to negative feedback by gonadal steroids. Recent studies have postulated the existence of ultra-short-loop negative feedback regulation for GnRH and have reported the partial purification of a hypothalamic factor that inhibits GnRH-stimulated LH release, adding to the complexity of the control of sexual function.

The factors that influence the onset of puberty are far from fully understood. The postnatal decline in serum gonadotrophin levels is thought to reflect the inhibitory influence of extrahypothalamic CNS centers upon hypothalamic GnRH secretion. Since Weinberger and Grant proposed an association between posterior hypothalamic lesions (including tumors) and precocious puberty, numerous reports have delineated hypothalamic lesions associated with sexual precocity. In 1950, Stotijn and Nauta reported the case of a 7-year-old boy whose precocious puberty was caused by a nondestructive hypothalamic hamartoma. A great diversity of tumors, in terms of both histology and size, have been reported to result in precocious puberty. They ranged from a tangerine-sized carcinoma of the ependyma of the third ventricle to a benign neoplasm the size of a large pea between the infundibular stalk and the carotid artery. Another case of precocious puberty resulted from a small retroinfundibular hamartoma that caused "little damage to the hypothalamic tissue."

Loci of hypothalamic lesions causing precocious pu-
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In the patient reported here, the coronal MR image revealed damage to the posterior hypothalamus, while the sagittal MR projection showed focal damage to the region of the mamillary bodies (Fig. 2). Putative inhibitory CNS centers that exert their restraining influence on the arcuate nucleus of the medial basal hypothalamus through the posterior hypothalamus remain to be identified.

Melatonin, the hormone secreted by the pineal gland, has a marked endogenously driven circadian rhythm. In all mammals studied thus far, including humans, plasma melatonin levels are five- to tenfold higher during the night than during the day. The pineal gland, long known to function as a neuroendocrine transducer, receives a sympathetic nervous input which is entrained by the daily exposure of the retina to environmental light (Fig. 4). Such sympathetic stimulation elicits the secretion of the antagonadotropic indole amine, melatonin. Signals from the eye reach the suprachiasmatic nucleus of the hypothalamus through specific retinohypothalamic projections. In experimental animals, the suprachiasmatic nuclei have
been shown to project efferents to the retrochiasmatic hypothalamus. It is thought that the signals then pass via the median forebrain bundle and midbrain reticular formation to the intermediate lateral cell column. Preganglionic fibers then pass to the superior cervical ganglion which projects to the pineal gland. Thus, the retinohypothalamic tracts serve as the conduit for photic regulation of the pineal enzymes N-acetyltransferase and hydroxyindole-O-methyltransferase.

Animal experimentation has implicated the pineal body as a suppressor of gonadotrophin release through the action of melatonin on the hypothalamus and the pituitary. In vitro administration of melatonin has been found to inhibit the pituitary gonadotrophic response to GnRH, while exogenous melatonin exerts an antigonadotrophic effect at the gonadal level. Melatonin may interfere with pubertal development through inhibition of GnRH secretion since melatonin administration suppresses the pubertal peaks of pituitary GnRH receptors and pituitary and plasma FSH levels. Furthermore, melatonin binding sites have been found in the hypothalamus. Inhibition of sexual maturation by melatonin administration or by changes in the photoperiod may be mediated by amplification of the photoperiodic restraint on LH secretion. Kitay has reported that destructive pineal tumors are associated with precocious puberty, while hyperplastic tumors result in delayed puberty.

Further circumstantial evidence of a role for melatonin in the control of human reproductive function comes from the finding that peak nocturnal serum melatonin levels decrease significantly with advancing development. A significant decrease in the day/night increment in serum melatonin from preschool age to older pubertal children was found by Waldhauser, et al. Circadian rhythmicity is preserved during the decline. In the case of our patient, the entrained circadian rhythm of melatonin with nocturnal elevation was lost. During the 24-hour period assayed, the actual values were lower than for adult women and peripubertal boys (Fig. 3). In light of our clinical, radiological, and laboratory findings, it is possible that the hypothalamic lesions interrupted one of the upper links of the descending pathway by which the hypothalamus, via the peripheral sympathetic nerve, affects the release of melatonin by the pineal gland. This apparent disconnection of the circadian rhythm could have been achieved in our patient through the interruption of the retinohypothalamic tract or damage to the suprachiasmatic nuclei or its efferents (Fig. 4).

The data presented in this paper also concur with those in the previously cited literature in defining the region of the mamilary body and tuber cinereum as central to the routing of this inhibitory influence. Whether the observed disturbances of melatonin release were coincidental, causative, or the effect of hypothalamic damage is conjectural. Determination of diurnal variation in body temperature would have been valuable since it would, if intact, indicate normally functioning hypothalamic regulatory centers and would further implicate the pineal as the cause of sexual precocity. This test was not performed because of persistent pyrexia caused by the patient's pneumonia. Although a wealth of circumstantial evidence supports a restraining role for the CNS in the regulation of puberty, such loci remain to be defined.

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References

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