Precocious puberty after traumatic brain injury

After traumatic brain injuries in 33 prepubertal children, precocious puberty was observed in seven. Precocious puberty developed significantly more frequently in girls than in boys (54.5 versus 4.5%, $P < 0.01$). Six children with precocious puberty were in coma for ≥2 weeks. Follow-up computed tomography revealed cerebral atrophy or focal encephalomalacia in all children with and 69% of children without precocious puberty. There were no striking differences in incidence of motor or cognitive deficits or posttraumatic epilepsy in children with and without precocious puberty. In four of five children, basal sex steroid levels were elevated, and the response to luteinizing hormone releasing hormone stimulation revealed a pubertal pattern after the appearance of secondary sex characteristics. (J PEDIATR 1987;110:373-7)

Joseph J. Sockalosky, M.D., Robert L. Kriel, M.D., Linda E. Krach, M.D., and Marian Sheehan, Ph.D.

From the Gillette Pediatric Head Injury Service of Gillette Children's Hospital and the St. Paul Ramsey Medical Center, St. Paul, Minnesota

Among the sequelae of severe head injury in early childhood, precocious puberty has been infrequently reported.[1-3] Head trauma is often listed as one of the causes of precocious puberty in both sexes, but the mechanisms involved are unknown.[4,5] In addition, apart from being stated to be a rare event, there are no data regarding the incidence, sex differences, or other factors related to premature sexual development after severe head injury.

We describe seven children in whom precocious puberty developed after traumatic brain injury.

METHODS

St. Paul Ramsey Medical Center/Gillette Children's Hospital is a regional acute trauma and rehabilitation center. From 1979 to 1985, 93 children were admitted to the center after traumatic brain injury. Of these, 11 girls and 22 boys were injured before onset of puberty. These children have been observed for 6 months to 6 years after their accidents.

Precocious puberty was defined as onset of secondary sex characteristics in girls before the age of 8.5 years and in boys before the age of 10 years.[6,7] When pubertal changes were first apparent, physical examination and laboratory data were obtained, including bone age, gonadotropin and estradiol or testosterone levels, thyroid function, and adrenal androgen levels. Luteinizing hormone releasing hormone stimulation tests[8,9] were performed within the first year after onset of pubertal changes in five children; in one of these the test was performed (as part of a prospective study) before the first clinical signs of pubertal development were noted. Follow-up bone age determinations and laboratory studies were obtained when indicated.

CT	Computed tomography
LH-RH	Luteinizing hormone releasing hormone

Computed tomography of the head was performed ≥2 months after injury in all 33 children and reviewed in a blind manner. The degree of atrophy for each cerebral hemisphere was scored on a scale ranging from 0 to 3, with

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Reprint requests: Joseph J. Sockalosky, M.D., Department of Pediatrics, St. Paul Ramsey Medical Center, 640 Jackson St., St. Paul, MN 55101.

Table I. Patient data: Children with precocious puberty

Patient	Sex	Age (yr)			Tanner stage		Bone age/chronologic age (yr)	
		At injury	At onset of puberty	At menarche	At initial evaluation	At follow-up	At initial evaluation	At follow-up
1	F	4.2	4.6	6.6	II Breast I Pubic hair	V Breast V Pubic hair	5.7/5.4	11/7.1
2	F	8.3	8.7		III Breast II Pubic hair	IV Breast IV Pubic hair	8.8/8.8	12/10
3	F	4.2	4.6		II Breast II Pubic hair	III Breast III Pubic hair	5.8/5.6	10.0/7.0
4	F	3.5	3.7		II Breast I Pubic hair	III Breast I Pubic hair	3.5/3.6	4.8/4.1
5	F	7.1	8	8.8	—	V Breast V Pubic hair	—	15/11.3
6	F	6.6	8	10	—	V Breast V Pubic hair	—	15/12.6
7	M	5.7	7.1		III Pubic hair III Penis Testes 8 cm^3	III Pubic hair III Penis Testes 10 cm^3	6/7.4	7.5/8.0

Table II. Baseline hormonal data

Patient	LH (mIU/ml)	FSH (mIU/ml)	Estradiol (pg/mL)	Testosterone (ng/dL)	DHEA (ng/dL)	DHEA-S (μg/dL)	T_4 (μg/dL)	TSH (mU/mL)	Prolactin (ng/mL)
1	5	5	25	—	1.3	13	11.4	2.1	16
2	<3	8	18	—	123	32	8.2	1.6	9.0
3	<3	4	<10	—	128	55	9.7	3.2	10
4	<3	9	15	—	6	<5	6.3	2.7	10
7	6	8	—	311	69	23	6.4	2.5	8.5
Normal prepubertal levels	<8	<3	<10	<20	31-345	10-60	5.6-13.3	0.6-5.0	1-20

DHEA(S), dehydroepiandrosterone (sulfate); FSH, follicle-stimulating hormone; LH, luteinizing hormone; T_4, thyroxine; TSH, thyroid stimulating hormone.

0 being normal and 3 indicating severe ventricular dilation with areas of encephalomalacia. The scores for the two hemispheres were added. In an effort to evaluate hypothalamic injury more specifically, third ventricle dilation was rated on a separate scale of 0 to 3, with 0 being normal and 3 indicating marked dilation.

Motor and cognitive function at most recent follow-up were rated using two separate scales of 0 to 5, with 0 being normal and 5 being comatose or no purposeful movements. Criteria for motor outcome included ambulation with or without devices, and ability to move from bed to chair or dependency on others. Cognitive scale criteria included amount of special education services, and severity of memory and behavior problems. Cognitive and motor ratings were made independently by two reviewers.

RESULTS

The 11 girls ranged in age at the time of injury from 2.1 to 8.3 years (mean 5.4 years), and the 22 boys from 2 months to 9.3 years (mean 4.6 years). Six (54.5%) of 11 girls and one (4.5%) of 22 boys have evidence of precocious puberty ($P < 0.01$).

Clinical data for the seven children with precocious puberty are summarized in Table I. The first signs of pubertal development were noted from 2 to 17 months after head injury. Three of the girls had early onset of menarche, within 2 years after the appearance of pubertal changes. In none of the patients was there a family history of early maturation or early menses, and there was no history of exposure to exogenous androgens or estrogens. Skeletal maturation at the time of onset of precocious puberty was equivalent to or less than chronologic age in the five patients in whom it was determined. Follow-up bone ages were significantly advanced in all patients observed for ≥ 2 years. Growth hormone testing was not performed, but linear growth velocity was increased above the mean for chronologic age in all patients.

Hormonal data are summarized in Table II. Patients 5

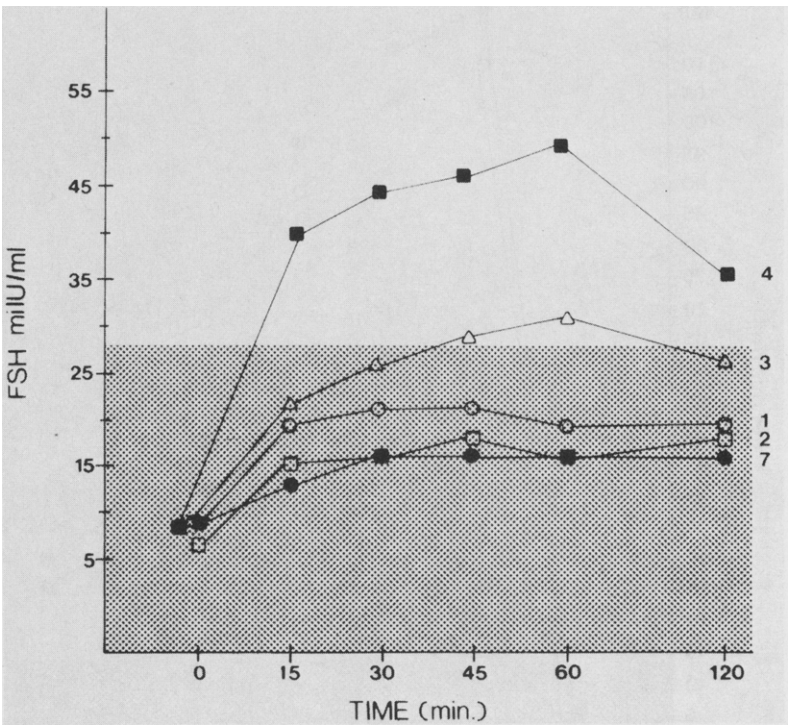

Fig. 1. Follicle-stimulating hormone response to intravenously administered luteinizing hormone releasing hormone, 100 μg, at time 0 in five children with precocious puberty. *Shaded area* represents normal peak response in prepubertal children.

and 6 were identified retrospectively, and no baseline data are available. Baseline gonadotropin levels were indistinguishable from prepubertal levels or were minimally elevated. Estradiol levels were elevated in patients 1, 2, and 4. The serum testosterone concentration in the one boy was elevated to the pubertal range. Baseline levels of adrenal androgens were within the prepubertal or early pubertal range in all patients tested. Thyroid function and prolactin levels were normal in all. The response to LH-RH stimulation was consistent with a pubertal pattern in all patients tested (Figs. 1 and 2).

Diabetes insipidus has been observed in three children with and two children without precocious puberty. It was transient in all but patient 4, who also has abnormal thirst regulation and poor appetite control. In the patients with transient diabetes insipidus, desmopressin acetate (DDAVP) was required for 1 to 4 months. No other endocrine abnormalities were seen in the children with precocious puberty. In the group without precocious puberty, one boy has panhypopituitarism.

The median duration of coma was not significantly longer in the girls with than in those without precocious puberty (21 vs 28 days). However, six of the seven children with precocious puberty were in coma at least 14 days. There were no significant differences in children with and without precocious puberty in ratings of cerebral atrophy or of cognitive or motor deficits. Third ventricle dilation was significantly worse in the children with precocious puberty ($P < 0.05$). Patient 4 had no dilation of the third ventricle, nor did she have diffuse cerebral atrophy, but CT scan showed a small area of encephalomalacia adjacent to the third ventricle, which occurred as a result of penetrating head injury. Two children with precocious puberty have posttraumatic epilepsy and are receiving anticonvulsant medication (phenytoin, carbamazepine); one boy and one girl without precocious puberty also have posttraumatic epilepsy.

DISCUSSION

Cognitive impairment, motor deficits, and seizures are the most commonly reported sequelae of traumatic brain injury.[10-12] There are few previous reports of precocious puberty after brain injury in children.[1-3] McKiernan[2] reported a boy in whom signs of precocious puberty developed at age 4 years; there was no detailed description of the severity of the injury but the patient was described as hyperactive, with no other neurologic abnormalities at follow-up. Shaul et al.[3] reported a boy and a girl with precocious puberty after head injury; initial CT scans were markedly abnormal. In one, follow-up CT scan showed

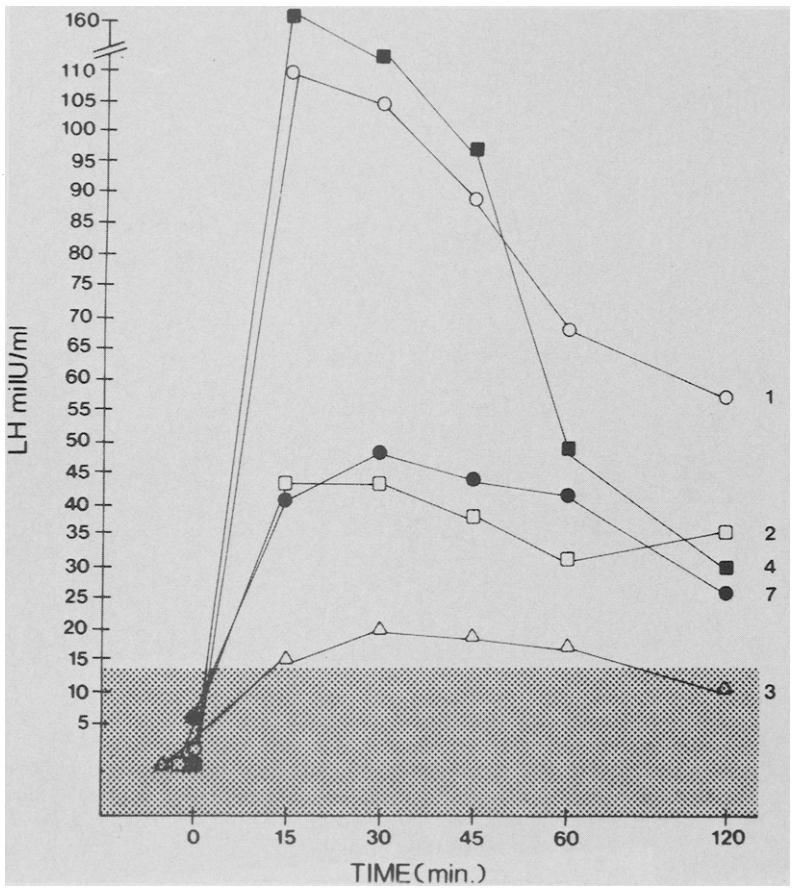

Fig. 2. Luteinizing hormone response to intravenously administered luteinizing hormone releasing hormone, 100 μg, at time 0 in five children with precocious puberty. *Shaded area* represents normal peak response in prepubertal children.

ventricular dilation and left frontal lobe atrophy. Neurologic outcome in these two children included quadriparesis, aphasia, and seizures in one, and hemiparesis and marked intellectual deficit in the other. Both patients had onset of precocious puberty within months of the acute injury. LH-RH stimulation studies revealed a marked increase in luteinizing hormone levels in both children. A girl reported by Sigurjonsdottir and Hayles[1] also had onset of pubertal changes within 5 months of a head injury. She was in coma for 5 months, and had severe mental retardation at follow-up. There are similarities between these case reports and our series, particularly with regard to neurologic outcome, CT scan abnormalities, timing of onset of precocious puberty after injury, and results of LH-RH stimulation testing.

In contrast to the previous reports of precocious puberty after traumatic brain injury, there was a marked female preponderance in our series. This female preponderance is also in contrast to the sex distribution reported by Balagura et al.[13] in precocious puberty of cerebral origin. It is, however, in accord with the higher frequency of precocious puberty in girls than in boys when all causes (idiopathic included) are considered.[14, 15] Whether the sex difference reflects a lower threshold for disruption of the factors regulating LH-RH release from the hypothalamus or earlier incipient maturation of the hypothalamic-pituitary-gonadal axis in girls remains speculative. The female preponderance we observed could not be explained by discrepancies in age or severity of brain injury. The one boy with precocious puberty was, however, one of three with hydrocephalus requiring a shunt; none of the girls have required shunt placement.

Patient 2 was included even though pubertal onset at age 8.7 years could be considered at the early extreme of normal. She had no signs of pubertal development at the time of injury, and had secondary sex characteristics before leaving the hospital. She has shown rapid progression of pubertal changes and advancement of skeletal maturation. Her mother's age at menarche was 14 years, and there was no family history of early development. We

believe that she experienced early and accelerated pubertal development as a result of head injury.

Our data suggest possible direct hypothalamic injury in our patients with precocious puberty, on the basis of third ventricle dilation and presumed atrophic changes in the hypothalamus. However, disruption of extrahypothalamic inhibition of LH-RH release in these patients also could explain the precocious development. At present, we do not fully understand the regulation of the onset of puberty in the normal child. It is thought that extrahypothalamic inhibition of LH-RH release is involved, but the nature of this inhibition and the mechanism underlying the release or escape from this inhibition remains undefined.[16, 17]

The overall frequency of precocious puberty in our series is striking. Furthermore, it should be considered a conservative estimate, because some children still at risk have not been observed for sufficient time to exclude the possibility of precocious development. Precocious puberty is occasionally encountered in other children with severe central nervous system insult, such as cerebral palsy and congenital hydrocephalus, but the incidence in these conditions would appear to be far below the 21% in our series.[1, 13, 18] We suspect that an increased awareness of the problem will lead to earlier and more frequent recognition of precocious puberty in children after severe traumatic brain injury.

The phenomenon of precocious puberty after severe head trauma in children has significant implications for patient management. The development of precocious puberty adds to the emotional and psychosocial problems faced by the patient and family. Inasmuch as the precocity is mediated through the hypothalamic-pituitary pathways, use of LH-RH analogue therapy should be effective in arresting pubertal progression.[19] We are presently evaluating the efficacy of LH-RH analogue therapy in our patients.

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