CT of Cerebral Abnormalities in Precocious Puberty

Kenneth G. Rieth[1]
Florence Comite[2]
Andrew J. Dwyer[3]
Mary Jo Nelson[4]
Ora Pescovitz[2]
Thomas H. Shawker[3]
Gordon B. Cutler[2]
D. Lynn Loriaux[2]

True precocious puberty occurs as a result of the premature release of luteinizing hormone-releasing hormone from the hypothalamus, which stimulates the secretion of the pituitary gonadotropins, which in turn stimulate the gonadal sex steroids. The differential diagnosis of true precocious puberty includes cerebral and idiopathic categories. This differentiation, which cannot be made endocrinologically due to similarities in pituitary gonadotropin and sex steroid levels, may be facilitated by high-resolution CT. A CT study of 90 children (73 girls and 17 boys) with true precocious puberty was performed at the NIH to detect cerebral causes of their precocious puberty. Thirty-four cerebral abnormalities were demonstrated in 32 children, 16 boys and 16 girls. These included hypothalamic hamartomas (17), hypothalamic astrocytoma (one), optic chiasm lesions (six), ventricular abnormalities (eight), arachnoid cyst (one), and teratoma (one). The CT appearance of these cerebral abnormalities is discussed and related to the endocrinologic findings and natural history of true precocious puberty. A practical neuroradiologic approach to the evaluation of children with precocious puberty is presented.

The onset of puberty coincides with the augmented nocturnal episodic pulsations of gonadotropins; specifically, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These pituitary hormone pulses are initiated by the release of luteinizing hormone-releasing hormone (LHRH) from the hypothalamus and result in gonadal sex steroid secretion, which causes the secondary sexual changes. By definition, puberty is "precocious" when sexual maturity begins before the age of 8 years in girls and 9 years in boys. The diagnosis is based on clinical history and physical examination, and is generally confirmed by hormonal assay and radiologic evidence of advanced bone age.

Precocious puberty is divided into two major categories, true or central precocious puberty and peripheral precocious puberty. The latter occurs with elevated levels of gonadal sex steroids independent of hypothalamic-pituitary activation. Peripheral precocious puberty may be secondary to congenital adrenal hyperplasia; McCune-Albright syndrome [1, 2]; familial male precocious puberty [3, 4]; neoplasms of the ovary, adrenals, or testes; and tumors that secrete human chorionic gonadotropin ectopically.

True precocious puberty is due to the premature release of pituitary gonadotropins. Clinically, this is associated with development of breasts, pubic hair, and menses in girls, and with testicular enlargement, pubic hair, and erections in boys [5, 6]. The bone age tends to be advanced, causing increased stature as a child and compromised adult height as a result of early epiphyseal closure.

Associated with true precocious puberty is an increased prevalence of CNS abnormalities. The reported histologic diagnoses have included hypothalamic hamartomas, gliomas, astrocytomas of the hypothalamic region, tumors of the pineal region, dysgerminomas, optic gliomas, and neurofibromas [7–27]. Although craniopharyngiomas are more frequently associated with delayed puberty, they have also been reported with precocious puberty [28–30]. Also, several nonneoplastic

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[1] Department of Radiology, The Fairfax Hospital, 3300 Gallows Road, Falls Church, VA 22046.

[2] Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Besthesda, MD 20892.

[3] Diagnostic Radiology Department, The Clinical Center, Bldg. 10, Rm. 1C660, National Institutes of Health, Bethesda, MD 20892. Address reprint requests to A. J. Dwyer.

[4] Department of Diagnostic Radiology, Veterans Administration Hospital, Minneapolis, MN 55417.

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cerebral processes have been associated with precocious puberty, including postinfectious states, hydrocephalus, suprasellar cyst, septooptic dysplasia, granuloma, head injury, tuberous sclerosis, and basilar artery aneurysm [31–36].

Owing to the anecdotal nature of case report data, it is probable that these observations include some coincidental associations. However, the clear increase in prevalence of CNS tumors together with their predilection for involvement of the hypothalamic region suggests a causal relationship. Moreover, the relatively high risk of detectable CNS abnormalities, some of which may have serious neurologic consequences, necessitates the differentiation of cerebral versus idiopathic precocious puberty. Save for findings directly related to the CNS lesions per se, cerebral and idiopathic cases are difficult, if not impossible, to distinguish clinically and endocrinologically. High-resolution cerebral CT facilitates this differentiation. This is a report of our experience at the NIH and a review of the literature.

Material and Methods

Patients referred to the NIH with a presumptive diagnosis of precocious puberty underwent sonographic, clinical, and endocrinologic evaluation. Sonography of the adrenals and pelvis was used to exclude peripheral precocious puberty secondary to adrenal or ovarian neoplasm. Ovarian size was also helpful in establishing complete precocious pubertal maturation and in excluding premature thelarche or precocious adrenarche [37].

In our series, 90 children (73 girls, 17 boys) had true precocious puberty. Ninety patients were studied with cerebral CT using a third-generation scanner (GE 8800). Contiguous precontrast scans of 5-mm slice thickness were obtained from the base of the brain to the level of the third ventricle. This was followed by intravenous contrast injection (Hypaque 60% 2 ml/kg) and repeat scanning at 5-mm thickness with 2.5-mm overlap covering the same area, then 10-mm contiguous scans to the top of the head. Image reformatting into sagittal and coronal planes was performed in the presence of abnormal axial CT scans. Children with abnormal cranial CT scans were followed at 6-month to 1-year intervals for 2 years after the initial study, and thereafter at 2-year intervals.

Endocrine evaluation included measurement of basal pituitary gonadotropins (LH and FSH), plasma estradiol, and testosterone. A standard LHRH stimulation test was obtained to determine the peak LH and FSH response. Plasma 17-hydroxyprogesterone and 11-deoxycortisol were measured to diagnose congenital adrenal hyperplasia. Human chorionic gonadotropin (HCG) levels were measured to exclude a tumor producing this hormone. Hormonal assays were run as previously described [38].

Results

Clinically, breast development (Tanner stages 2–5) [39] was present in all the girls and pubic hair was present in some. Testicular development, 7–25 ml by Prader orchiodometer (greater than 6 ml is pubertal), and pubic hair (Tanner stages 2–5) were present in all the boys. Scant facial and axillary hair was present in many of the boys. Spontaneous erections had occurred in all cases.

Endocrinologic evaluation documented increased plasma levels of pituitary gonadotropins, augmented nocturnal gonadotropin pulsations, and a pubertal response to the LHRH stimulation test (an increase in plasma LH that exceeded the increase in plasma FSH) [38].

Mean estradiol levels were elevated in the girls and testosterone levels were elevated in the boys, ranging from 50 to 1000 nanograms per deciliter. Plasma 17-hydroxyprogesterone and 11-deoxycortisol levels were normal in all but one of the children, who had coexistent 21-hydroxylase deficiency and central precocious puberty from a ventricular cyst. HCG levels were normal in all children.

CT and sonographic examinations of the adrenal glands were normal in the first 50 cases. Only one child referred to the NIH had an abnormal adrenal CT scan, which was secondary to a feminizing adrenal tumor [40].

Pelvic sonography in the girls documented postpubertal uterine and ovarian development. Uterine dimensions averaged 5.6 cm × 2.4 cm. Ovarian volume averaged 3.2–3.5 cm^3.

Cerebral CT scan was obtained in all 90 children. Sixteen (94%) of the 17 boys and 16 (22%) of the 73 girls had cerebral abnormalities detected by CT scanning.

Hypothalamic Masses

Nine boys (53%) and 8 girls (11%) had lesions in the area of the tuber cinereum. CT revealed a mass equivalent in density to brain (30–40 Hu) located posterior to the infundibulum and optic chiasm and extending into the interpeduncular, prepontine, and posterior suprasellar cisterns. These masses showed no contrast enhancement (Fig. 1). One of the scans revealed calcification within the mass (Fig. 2). Sagittal and coronal reformatted scans in several cases revealed the pedunculated nature of these tumors (Fig. 3). In one girl, secondary hydrocephalus was associated with the hypothalamic mass due to obstruction at the level of the cerebral aqueduct. The hypothalamic masses ranged in size from 0.5–3.5 cm, and 14 were smaller than 2.0 cm in diameter. Eleven of the 17 tumors were discovered before the age of 3 years. The average age of presentation was 2.8 years, with a range of 6 months to 8 years. On the average, girls presented slightly earlier (2.5 years) than boys (3.4 years). A tissue diagnosis of hamartoma was obtained in four patients. Neither growth nor regression of any of the masses was noted over follow-up periods ranging from 6 months to 4 years.

One 2-year-old girl in our series had a 1½-cm lesion in the region of the hypothalamus that resembled a teratoma and contained fat, calcification, and an area of soft-tissue density equivalent to brain, which demonstrated contrast enhancement (Fig. 4). This child also had a "prominent" pineal gland with minimal contrast enhancement. It is uncertain whether the pineal abnormality was present on the patient's earliest scans, but neither area showed any change over a 2-year follow-up.

Chiasmal Lesions

Masses related to the optic chiasm and anterior hypothalamus were seen in seven patients: five boys and two girls.

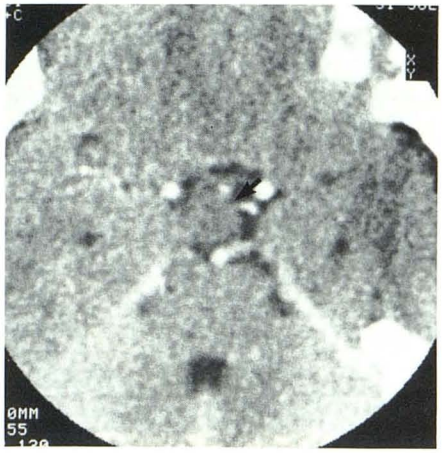


Fig. 1.—Nonenhancing soft-tissue mass (*arrow*) of brain density in suprasellar cistern situated between enhanced pituitary infundibulum and basilar artery.

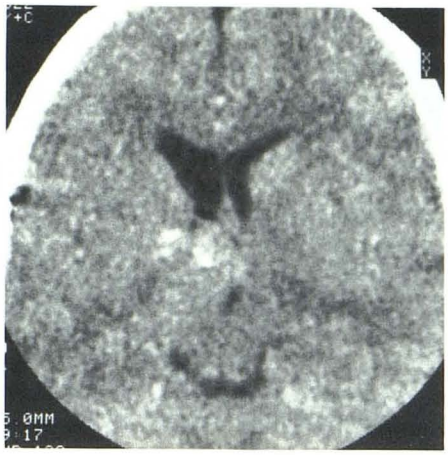


Fig. 2.—Biopsy-proven calcified hypothalamic hamartoma compresses third ventricle. No enhancement is noted.

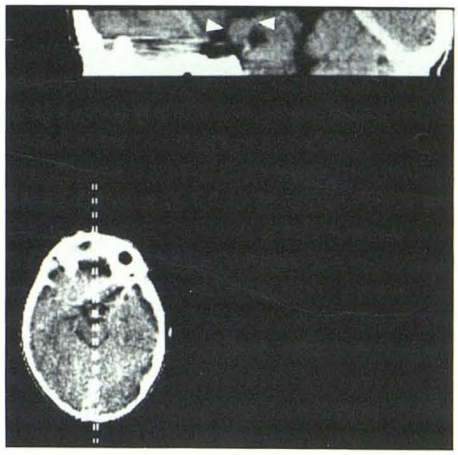


Fig. 3.—Baseline sagittal reformation of axial image reveals pedunculated mass originating in hypothalamus (*arrowheads*).

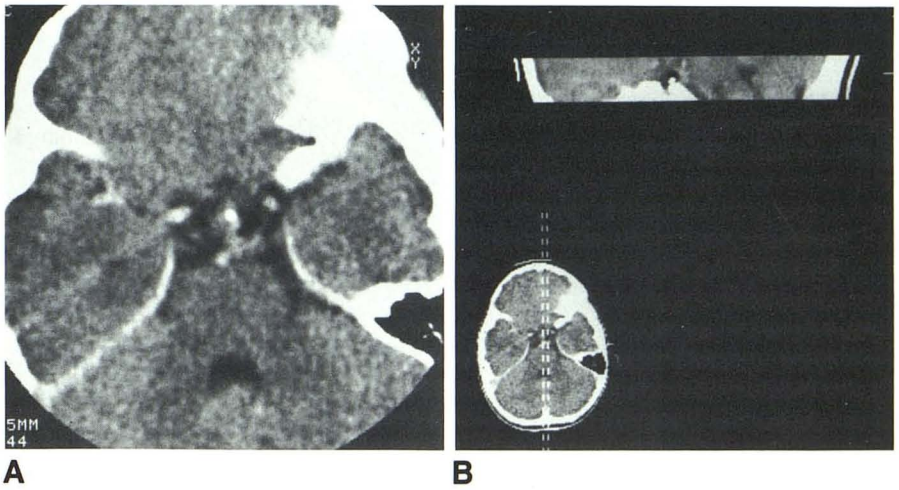


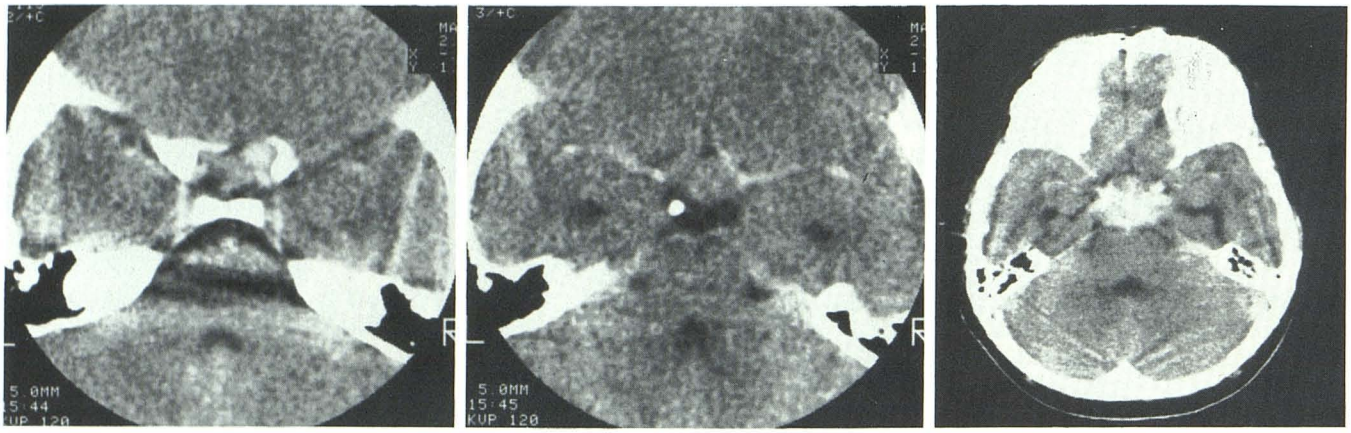
Fig. 4.—Axial (*A*) and sagittal (*B*) CT scans demonstrate 1-cm mass containing fat, calcium, and enhancing soft tissue above dorsum sella in interpeduncular cistern, presumably representing a teratoma.

CT in all cases revealed a mass equivalent to or slightly greater than brain density before contrast. In two cases, calcification was present. All lesions demonstrated contrast enhancement. In five patients only a portion of the mass enhanced (Fig. 5) while in two patients enhancement was homogeneous (Fig. 6). The masses partially or completely filled the suprasellar cisterns. One extended superiorly to involve the septum pellucidum and one involved the optic nerve unilaterally. Sagittal and coronal reformatted images were helpful in distinguishing the parachiasmal and hypothalamic location of the masses (Fig. 7). Secondary hydrocephalus occurred in three patients with obstruction in the region of the foramen of Monro. Visual symptoms preceded the development of precocious puberty in all but two cases. Radiation therapy (4500–5000 R) had been given in three of the seven cases before the onset of sexual precocity. The onset of puberty in these cases was later than in children with hypothalamic hamartomas, and ranged between 3 and 9 years with an average of 6.5 years. Four of the seven masses were surgically proven to be optic gliomas. Two of these, one boy and one girl, had neurofibromatosis.

Follow-up scans ranging from 6 months to 2 years were obtained in four patients. In one patient with neurofibromatosis, growth of the mass was noted (Fig. 8), whereas the others remained stable.

Ventricular and Cisternal Abnormalities

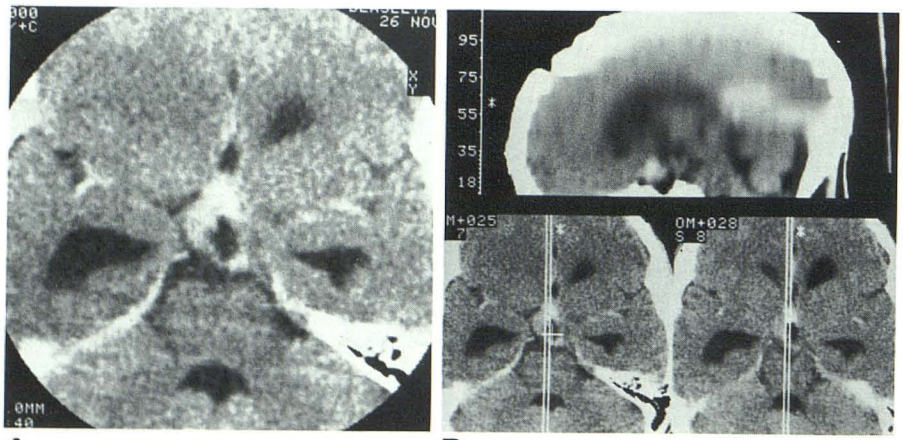
Abnormalities related to the ventricles and subarachnoid cisterns were present in nine cases. Eight had hydrocephalus, three of which required shunting. Five, three girls and two boys, had secondary hydrocephalus due to obstruction in the region of the third ventricle or cerebral aqueduct from optic gliomas (two cases), hypothalamic hamartoma, hypothalamic



A B

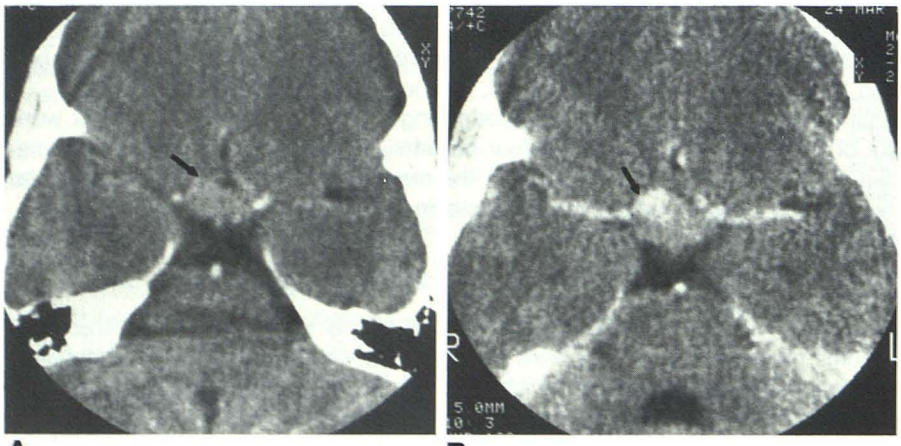
Fig. 5.—*A*, Lesion involving optic chiasm shows area of enhancement adjacent to eroded right anterior clinoid process.
B, Scan at higher level with mass in chiasmal region of suprasellar cistern.

Fig. 6.—Homogeneous contrast enhancement of lesion filling suprasellar cistern and involving optic chiasm.



A B

Fig. 7.—*A*, Astrocytoma grade 1 involving hypothalamus shows contrast enhancement around area of low attenuation.
B, Sagittal reformation places lesion inferior to third ventricle.



A B

Fig. 8.—*A*, Minimal contrast enhancement in lesion lying anterior to infundibulum and involving optic chiasm in patient with neurofibromatosis.
B, Comparable scan 9 months later establishes growth of mass with further enhancement along right anterior margin.

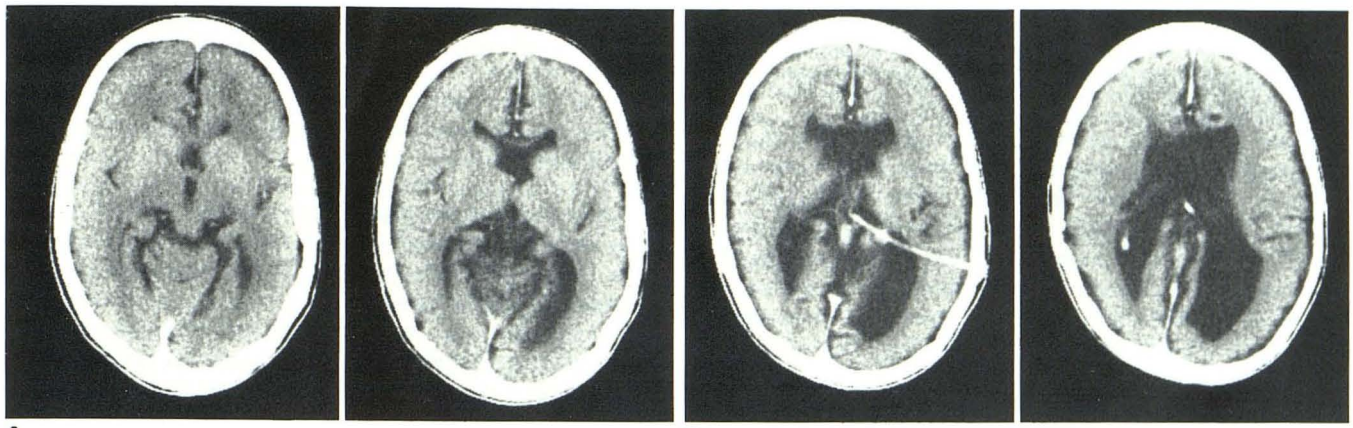


Fig. 9.—*A* and *B*, Arnold-Chiari II malformation in girl with precocious puberty. Prominent caudate nuclei indent frontal horns of asymmetrically dilated lateral ventricles with absent septum pellucidum. Prominence of massa intermedia and widened tentorial hiatus are present, as is midbrain asymmetry.

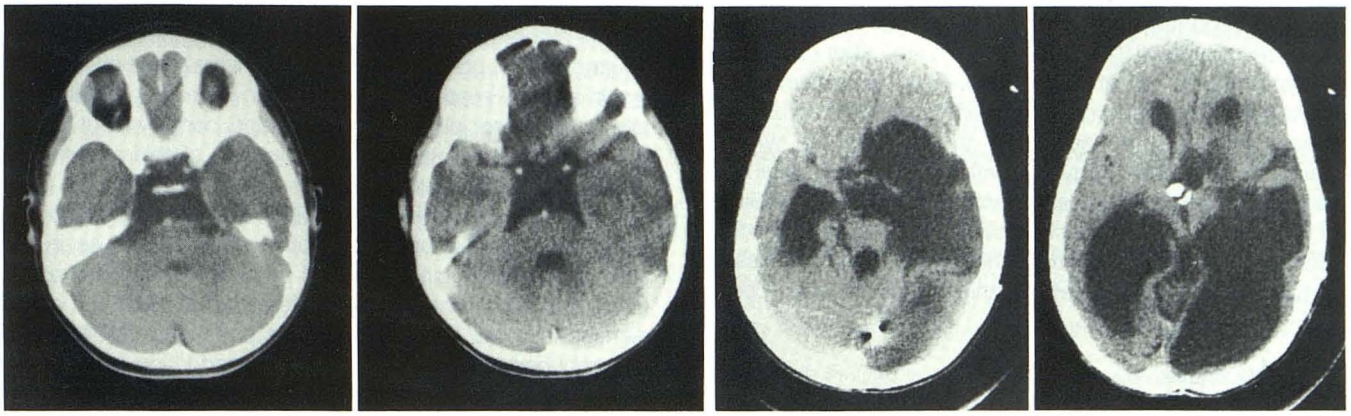


Fig. 10.—Enlargement of suprasellar and prepontine cisterns with "squaring" of borders in child with biopsy-proven suprasellar arachnoid cyst and precocious puberty.

Fig. 11.—Hydrocephalus and arachnoid cyst with suprasellar calcification in child with previous history of resection of "cyst on the third ventricle."

astrocytoma, or third-ventricular cyst, respectively. Three girls had Arnold-Chiari type II malformations (Fig. 9), one with associated encephalocele. One additional patient had a cavum septum pellucidum, and one girl had a suprasellar subarachnoid cyst (Fig. 10). The onset of precocious puberty in this group ranged from 18 months to 10 years, averaging 5.1 years. One patient had bizarre ventricular abnormalities and a history of a previously resected third-ventricular cyst (Fig. 11).

Discussion

Fundamentally, this series reiterates the increased prevalence of CNS tumors in patients with precocious puberty and indicates the need for cerebral CT in their work-up. The prognostic and therapeutic implications of a CNS lesion depend on its location and histology.

Hypothalamic Hamartoma

Hypothalamic hamartomas are foci of ectopic gray matter containing neurons, fiber bundles, and glial cells in appropriate proportion, originating in the posterior hypothalamus between the tumor cinereum and the mammillary bodies. Rarely, calcifications may be found within the hamartoma [33] as in one of our cases. The tumors range in size from several millimeters to several centimeters, but are usually smaller than 2 cm. Most often, the hamartomas are attached by a pedicle to the hypothalamus. They may arise, however, from the floor of the third ventricle, or may lie free in the interpeduncular fossa [7–25]. Slow growth has been described in these tumors [14], but this has not been our experience. No change in the size of the hamartomas or new neurologic abnormalities were noted with follow-up to 4–5 years. Other series have reported no change in follow-ups of up to 11 years [25–27].

Although hypothalamic hamartomas usually result in sexual precocity alone, neurologic signs, including gelastic seizures, may result from obstructive hydrocephalus or compression of adjacent structures by the larger tumors [15].

Hypothalamic hamartomas occur in both sexes, but are statistically more common in males, accounting for 58–64% of cases [3, 18]. In our series, nine (53%) of 17 males and eight (11%) of 73 females had a hypothalamic hamartoma. Usually, the onset of puberty occurred before the age of 3 years. The true incidence of hypothalamic hamartomas is not known, as these lesions may be asymptomatic. Likewise, the percentage of hamartomas presenting as precocious puberty is not known.

Surgical treatment of hypothalamic hamartomas remains controversial. Results of craniotomy have been reported in 10 patients, with partial removal of hamartomas in nine, and total removal in one [8, 11, 13, 14, 19–21]. Adjunctive radiotherapy was administered in two cases and hormonal suppressive treatment in seven [13, 21]. Five cases had slowing of sexual maturation with transient decrease in pituitary gonadotropin and sex steroid levels. However, only one case has been reported in which total reversal of symptoms was noted after surgery [21]. Three children died after craniotomy for hypothalamic hamartomas [14, 22]. In our series, four of 17 patients have had craniotomy and biopsy of hamartoma without significant morbidity and no mortality, but with no change in symptomatology and with continued pubertal maturation. The diagnosis of hamartoma is sufficiently specific on CT to eliminate the need for biopsy confirmation. Longer-term follow-up in association with a benign clinical course is essential to document the apparently benign nature of this process.

Chiasmal Lesions

Gliomas of the optic chiasm and hypothalamus may be associated with neurofibromatosis [34], as in two of our cases. These tumors are more commonly present in children, with boys being more often affected. This was similar to our results, as five boys and only two girls had this diagnosis. When gliomas are associated with precocious puberty, the onset of puberty is generally later than with hypothalamic hamartomas, 5.4 years for gliomas compared with 2.8 years for hamartomas. Three of our seven patients underwent radiation before the onset of precocious puberty. Complete surgical resection of optic glioma or hypothalamic astrocytoma is not possible, and neither partial resection nor radiation therapy appears to affect the course of the sexual precocity. However, specific diagnosis of tumors related to the optic chiasm may be important, as suprasellar germinomas, which may resemble optic gliomas and cause precocious puberty, are radiosensitive tumors [26]. Serum hCG should be measured in such patients because of the observation that ectopic hCG production is the mechanism of precocious puberty in many CNS germinomas [41]. A clinical differential finding may be the frequent association of diabetes insipidus in germinomas.

One patient with neurofibromatosis and an optic glioma showed tumor growth on follow-up scanning over a 2-year period. In this child, no significant change was noted in visual acuity, visual fields, or on neurologic examination.

Ventricular, Cisternal, and Miscellaneous Cerebral Abnormalities

CT scanning in this group clearly depicted the CSF spaces. The incidence of Arnold-Chiari II malformations in our series was unexpected and has not been previously reported. No change in CT appearance in this group was noted on subsequent examinations. Shunting of the ventricles and subarachnoid cyst had no demonstrable endocrinologic effect.

Curiously, only one of our patients had demonstrable abnormality in the pineal region, considering the relative frequency of pineal abnormalities reported in the literature in association with precocious puberty [13, 41].

Eight of the 58 children with presumed idiopathic true precocious puberty underwent repeat CT examinations 1 year after the initial examination. No CT abnormalities were found in this group.

The association between precocious puberty and CNS tumors along with their propensity to involve the hypothalamic pituitary axis suggests a causal relationship between the CNS lesion and the precocious puberty. However, the pathophysiology of precocious puberty remains controversial and a detailed discussion is beyond the scope of this report. The reader is referred to the excellent review by Balaguera et al. [13]. In brief, cells containing LHRH occur in the region of the anterior hypothalamus and preoptic area as well as in the area of the tuber cinereum and arcuate nuclei. Mechanical pressures from tumors may interfere with the function of the diencephalon via interruption of the pathways that normally (in prepubertal children) inhibit the production of pituitary gonadotropins from the median eminence, considered to be the site responsible for the onset of puberty [13]. Another theory is that the tumors mechanically stimulate the LHRH center [11]. In the case of hypothalamic hamartomas, the demonstration of neurosecretory granules in the tumor has lead to the postulate that the hamartoma itself may produce LHRH [8].

Some information about the natural history of precocious puberty is available. In a Mayo Clinic study [23] of 96 children (72 girls and 24 boys), five boys and 54 girls were thought to have idiopathic precocious puberty and were followed for periods ranging from 8 to 29 years. All patients in this group remained in good health. In the same study, among 15 boys with cerebral causes of precocious puberty, three died. The diagnoses in these cases were pinealoma, hypothalamic teratoma, and basilar artery aneurysm. Only two of the 15 boys with cerebral causes were self-sufficient as adults. Four of the 18 girls with cerebral causes of precocious puberty died. Their diagnoses included hypothalamic astrocytoma and cystinosis. Two died from unknown causes. Of the 14 remaining girls, 11 had problems secondary to the brain abnormalities. In this series, it is noteworthy that none of the "expanding" lesions of the hypothalamus were thought to be hamartomas, and none of the patients who died had hypothalamic hamartomas.

Medical Therapy

Medical therapy of precocious puberty has included antagonizing the effects of sex steroid with antiandrogens or suppressing gonadal secretion with progestins. Neither has been particularly successful. Recently, daily administration of synthetic analogues of LHRH have met with success in treating this disorder [38, 42]. The LHRH analogues initially stimulate, but later suppress, pituitary gonadotropin release by a presumed mechanism of uncoupling pituitary stimulation and response. At this time, this mechanism is not understood. The majority of our patients are receiving an LHRH analogue with a treatment duration from several months to 4 years. This treatment has normalized the hormonal levels and caused regression of the secondary sexual characteristics in many cases. The rapid linear growth and bone-age maturation have reverted to normal prepubertal rates among those receiving LHRH analogue therapy [43]. Additionally, no change in the CT appearance of the cerebral abnormalities has been detected in approximately 4 years of LHRH analogue administration.

In the absence of CT, it is difficult to distinguish idiopathic from cerebral causes of true precocious puberty. However, in children with onset of symptoms before 2 years of age, and in girls with unusually early menstruation, cerebral pathology is likely. A recent report of young girls with hypothalamic hamartoma [27] is substantiated by our experience. Boys, in general, have a much higher incidence of CNS abnormalities. Only one case in our series had idiopathic precocious puberty.

Conclusions

Based on our experience, a reasonable neuroradiologic approach to patients with precocious puberty would include high-resolution CT scan, before and after intravenous contrast material, to exclude cerebral causes in all children with true precocious puberty. Cerebral causes of precocious puberty are particularly likely in children presenting earlier than age 3 years. If the head CT is normal, no additional scanning is necessary and idiopathic precocious puberty is presumed. In those patients in whom a hypothalamic mass is discovered, no additional scans are needed unless a change in symptoms occurs, as these tumors, presumably hamartomas, do not show growth. Patients in whom CT suggests optic gliomas and hypothalamic astrocytomas require careful clinical follow-up and serial CT examinations to detect tumor growth. The demonstration of primary or secondary hydrocephalus may require shunting with sequential scanning dependent upon clinical outcome.

LHRH analogues, although effective in controlling the endocrine consequences of precocious puberty, do not appear to affect the CT scan appearance, regardless of cerebral or idiopathic origin.

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