Precocious Puberty Associated with a Pineal Cyst: Is it Disinhibition of the Hypothalamic-Pituitary Axis?

Rob D. Dickerman, Qualls E. Stevens, Jean-Alex Steide & Steven J. Schneider

Department of Neurosurgery, North Shore University-Long Island Jewish Medical Center, New Hyde Park, NY 11004, USA

Correspondence to: Rob D. Dickerman, D.O., Ph.D.
Department of Neurosurgery
260-12 74th Avenue
Glen Oaks, NY 11004
TEL: 516-354-3401
FAX: 516-354-8597
EMAIL: drrdd@yahoo.com

Submitted: March 25, 2004 *Accepted: April 12, 2004*

Key words: **precocious puberty; pineal cyst; neuroendocrinology; steroids, gonadal hormone**

Neuroendocrinol Lett 2004; ***25****(3):173–175 NEL250304C01 Copyright © Neuroendocrinology Letters* ***www.nel.edu***

CASE REPORT

Introduction

Accelerated development of secondary sexual characteristics or sexual precocity is a well-known entity [1–3]. Most authors recognize two groups of patients, those described as having central precocious puberty (CPP) and those with precocious pseudopuberty [1–3,6]. CPP results from premature activation of the hypothalamic-pituitary-gonadal axis and pseudopuberty is caused by lesions that secrete gonadotropin-like substances or hormones [6]. The onset of CPP is usually before age 8 in females and age 9 in males; however, there is contention that the age of onset is much earlier and also differs depending on the patients' race [2]. Previously reported causes of CPP include intracranial neoplasm, infection, trauma, hydrocephalus [3,4,5,6] and Angelman's syndrome [8]. Pineal cysts are usually asymptomatic incidental findings, but have been associated with CPP [1,3]. We present an interesting case of a patient with CPP and an associated pineal cyst. We review the literature on the pathogenesis of CPP and associated pineal cyst, the neuroendocrine relationship between the pineal gland and puberty and the neurosurgical role in these cases.

Case Report

A seven year-old female was referred to the neurosurgery clinic for evaluation of pineal cyst, headaches and precocious puberty. The patient had been thoroughly examined by pediatric endocrinology with the diagnosis of central precocious puberty with elevations in luteinizing hormone (LH), follicle stimulating hormone (FSH) and subsequent elevations in sex steroids. All other pituitary hormones were normal. Upon examination, there was obvious physical development beyond her years with evidence of breast development, axillary and pubic hair; she was Tanner stage 3, no menarche. Neurological examination was grossly intact other than a history of daily debilitating periodic frontal and occipital headaches. The patient's visual fields and extraocular muscles were intact without any evidence of Parinaud's syndrome. Magnetic resonance imaging revealed a pineal cyst approximately 1.4 cm x 1. 3 cm (Figure 1). Based on her physical examination, history of headaches and evidence of precocious puberty, we decided to surgically intervene with the thought that cystic decompression may stop the head-

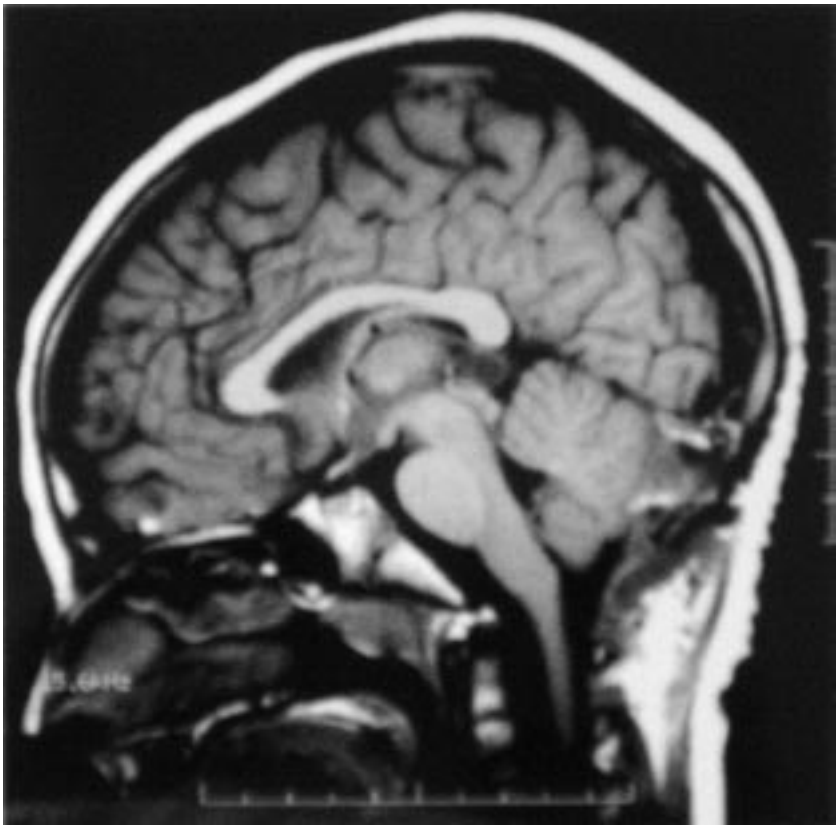

Figure 1. Preoperative sagittal T1-weighted magnetic resonance image of the brain demonstrating a 1 cm cystic lesion with mass effect on the pineal gland.

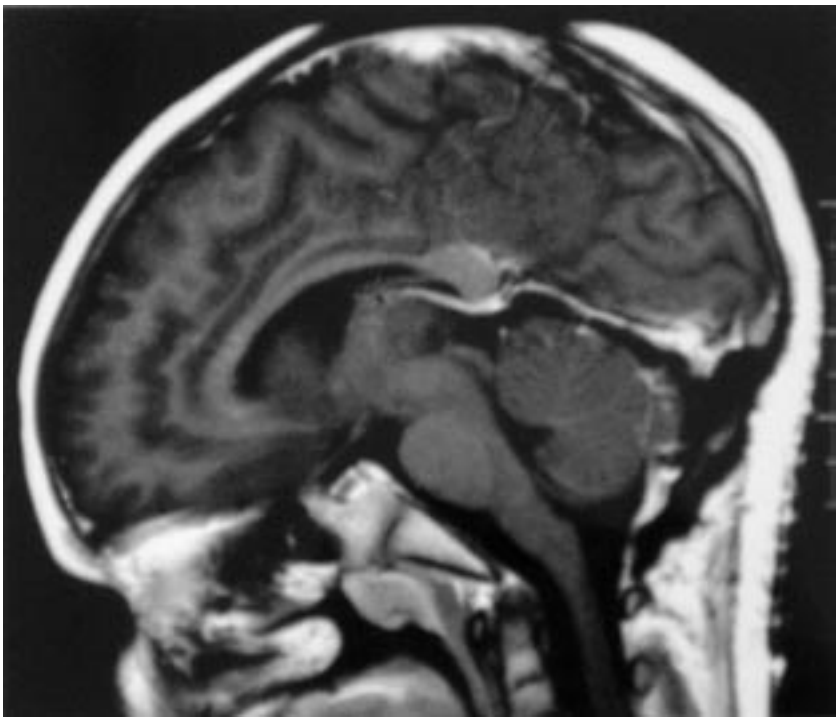

Figure 2. Postoperative sagittal T1-weighted magnetic resonance image of the brain demonstrating gross total resection of the cyst and decompression of the pineal gland.

aches and hopefully allow for normal progression in development. The patient underwent a standard suboccipital craniotomy, infratentorial/supracerebellar approach to the pineal gland. Precentral cerebellar veins had to be sacrificed for exposure. The cyst was evacuated via 20-gauge angiocath needle for later analysis of the cystic fluid for gonadotrophic-releasing hormones. The cyst capsule was taken en bloc without difficulty and gross visualization of the gland revealed some distortion from the cyst's mass effect (Figure 2). Neuropathological analysis revealed a multilayered pineal cyst consisting of an outer layer of islets of pineal tissue with fibrillar stroma forming rosettes surrounding a thick layer of neural tissue with numerous Rosenthal fibers. The cystic fluid was sent for radioimmunoassay of LH, FSH and gonadotropin releasing hormone (GnRH), all of which were negative. The patient tolerated the procedure well and was discharged home on postoperative day three. At six month follow-up, the patient denied headaches and had been started on Leuprolide (Lupron), a GnRH agonist, immediately postoperatively by pediatric endocrinology to insure cessation of puberty.

Discussion

Sexual precocity secondary to pineal masses is more common in females and these cases are usually idiopathic; however, there are two literary reports of pineal cysts associated with CPP [1,3]. A review by Mamorian et al., on 672 patients with pineal masses revealed an incidence of cystic lesions to be 4.3% and other authors have reported similar incidence [7,9,10]. A thorough history and physical examination is essential in the evaluation of any patient presenting with sexual precocity. Pineal masses are classically associated with headaches, paralysis of upward gaze or Parinaud's syndrome and hydrocephalus [13,17]. Pediatric endocrinology involvement is essential in the initial work-up with hormonal analysis and Tanner staging for the diagnosis of premature sexual advancement [5,6]. Neuroimaging modalities have greatly improved

the timely diagnosis of intracranial causes of precocious puberty. The sensitivity of MRI supersedes that of computed tomography in detecting pineal gland lesions [1,9,11]. It is important to differentiate pineal gland cysts from tumors, usually glial, with a cystic component as this precludes unwarranted therapies [10–12,16].

Many authors advocate those patients with cysts less than 1 cm and asymptomatic should be observed and followed with serial neuroimaging studies [3,10,16–18]. However, for the symptomatic cases such as ours, surgical resection of the cyst is indicated [16,17]. Medical therapy usually consists of Leuprolide, a long-acting GnRH agonist, which alters GnRH receptors and the production of serum gonadotropins. This is routinely used either pre- or post-operatively and has been reported to halt menses and any further development of secondary sexual characteristics in female patients with CPP [2,3,8]. The use of chemotherapy or radiation therapy for benign pineal cysts is not advocated and likely will result in untoward sequelae [16,17].

There have been several reports of pineal tumors, usually teratomas, being related to precocious puberty in patients and there are only two previous cases of pineal cysts and precocious puberty [1,3 6,7,13,14]. There are also a number of cases of precocious puberty and hypothalamic hamartomas [14,18,19]. A recent report on patients with precocious puberty and suprasellar and pineal lesions concluded that the onset of puberty is not from inhibition, but rather stimulation via a secretory product analogous to GnRH [20]. The exact cause of CPP remains controversial. One theory suggests the entity results from a pressure phenomenon exerted by the pineal lesions on the hypothalamic-pituitary-gonadal axis [14,15]. Others have argued that there is removal of the gonadotropin inhibition by melatonin [15]. Commentz reported on a case with CPP and low serum levels of melatonin [18]. Melatonin has been advocated as having a formidable role in the development of central precocious puberty; however, this theory has fared well in animal models and not their human counterparts [5,6]. Fetell et al., maintain that sexual precocity is due to the secretion of gonadotropins or gonadotropin-like substances by some pineal tumors [5].

We postulate the pineal cyst did not directly stimulate the hypothalamic-pituitary axis. Rather the inhibitory effect of the pineal gland on the release of gonadotropins was lost; hence, there was an increase in our patient's gonadal hormones. This was likely due to the size of the cyst and the alterations in the functional capacity of the gland. Our attempts in the analysis of the cystic fluid for GnRH were unsuccessful, although there could have been a GnRH analogue undetected by our assay.

In summary, precocious puberty related to pineal cysts is unclear, a lack of disinhibition via mass effect from the cyst is a plausible explanation. The initial diagnosis and work-up of precocious puberty should involve pediatric endocrinology and neurosurgery in concerted effort to treat these patients. Preoperative laboratory analysis can assist with identifying central precocious puberty. While no direct relationship was established in this case between the pineal cyst and precocious puberty, we demonstrate another case of precocious puberty coexisting with a pineal cyst. We feel that neurosurgical intervention was appropriate in this case for alleviating the headaches and hopefully assisting in cessation of the accelerated progression of puberty. This case exemplifies the need for continuing research in the field of neuroendocrinology, especially the role of the pineal gland in puberty.

REFERENCES

1 Kornreich L, Horev G, Blaser S, Daneman D, Kauli R, Grunebaum M. Central precocious puberty: evaluation by neuroimaging. Pediatr Radiol 1995; **25**:7–11.
2 Root AW. Precocious Puberty. Pediatr Rev 2000; **21**(1):10–9.
3 Franzese A, Buongiavanni C, Belfiore G, Moggio G, Valerio G, Ciccarelli NP et al. Pineal cyst in a girl with central precocious puberty. Clin Pediatr 1997; **36**(9):543–5.
4 Ilgren E, Briggs M, Aynsley-Green M. Precocious puberty in a 3-year-old girl associated with a parasellar ganglionic hamartoma. Clin Neuropathol 1983; **2**(2):95–8.
5 Fetell MR, Stein BM. Neuroendocrine aspects of pineal tumors. Neurologic Clinics 1986; **4**(4):877–905.
6 Cloutier MD, Hayles AB. Precocious puberty. Adv Pediatr 1970; **17**: 125–38.
7 Portillo ML, de Gonzalez CM, Sangines JB, Zapata GS. Pineal region tumors. Int Surg 1982; **67**(4):329–33.
8 Young C, Wang P-J, Tsai W-Y, Shen Y-Z. Precocious puberty in a case with probable Angelman syndrome. Brain Dev 1994; **16**(3):249–52.
9 Mamourian AC, Towfighi J. Pineal cysts: MR imaging. AJNR 1986; **7**(6):1081–6.
10 Golzarian J, Baleriaux D, Bank WO, Matos C, Flament-Durand J. Pineal cyst: normal or pathological? Neuroradiology 1993; **34**(4): 251–3.
11 Fleege MA, Miller GM, Fletcher GP, Fain JS, Scheithauer BW. Benign glial cysts of the pineal gland: unusual imaging characteristics with histologic correlation. AJNR 1994; **15**(1):161–6.
12 Tamaki N, Shirataki K, Lin TK, Masumura M, Katayama S, Matsumoto S. Cysts of the pineal gland. A new clinical entity to be distinguished from tumors of the pineal region. Childs Nerv Sys 1989; **5**(3):172–6.
13 Cohen AR, Wilson JA, Sadeghi-Nejad A. Gonadotropin-secreting pineal teratoma causing precocious puberty. Neurosurgery 1991; **28**(4):597–602.
14 Jones KL. Feminization, virilization, and precocious sexual development that results from neoplastic processes. Ann N Y Acad Sci 1974; **230**:195–203.
15 Penza JF, Charles D. Role of the hypothalamus in menstrual disorders. Clin Obstet Gynecol. 1969; **12**(3):786–99.
16 Klein P, Rubinstein LJ. Benign symptomatic glial cysts of the pineal gland: a report of seven cases and review of the literature. J Neurol Neurosurg Psychiatry 1989; **52**:991–995.
17 Wishoff JH, Epstein F. Surgical management of symptomatic pineal cysts. J Neurosurg 1992; **77**:896–900.
18 Commentz JC, Helmke K. Precocious puberty and decreased melatonin secretion due to a hypothalamic hamartoma. Horm Res 1995; **44**:271–275
19 Luo S, Li C, Ma Z, Zhang Y, Jia G, Cheng Y. Microsurgical treatment for hypothalamic hamartoma in children with precocious puberty. Surg Neurol. 2002 ; **57**(5):356–362.
20 Rivarola, Belgorosky A, Mendilaharzu H, Vidal G. Precocious puberty in children with tumours of the suprasellar and pineal areas: organic central precocious puberty. Acta Paediatr 2001; **90**(7): 751–6.