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A case of late presentation of precocious puberty due to pituitary astrocytoma

Późne rozpoznanie przedwczesnego pokwitania związanego z obecnością gwiaździaka przysadki. Opis przypadku

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Abstract

The importance of assessing precocious puberty, especially in boys, is not only due to the great complications it has for the affected patients, but also to the fatal underlying diseases. Therefore, children with central precocious puberty should first undergo neuroimaging. In this case study, we present a 9.5-year-old boy who was referred to Rasoul-e-Akram Medical Center with increased intracranial pressure, nausea/vomiting, and severe headache having begun three months earlier. The development of secondary sexual changes had started two years earlier, and had been neglected. His testes, penis, and pubic hair were at the fourth Tanner stage. He had elevated luteinizing and follicle stimulating hormones. Microscopic evaluation confirmed low-grade pilocytic astrocytoma WHO grade 1. Emergency brain surgery was conducted in which the brain was decompressed, and chemotherapy was started postoperatively. Two years after the surgery, he remains under chemotherapy, with obvious sexual maturation and a height of 154 cm. Training families and medical staff efficiently can help prevent the late diagnosis and treatment of precocious puberty and, as a result, help patients in their social life.

Key words: puberty, precocious, central

Streszczenie

Ocena przedwczesnego pokwitania, szczególnie występującego u chłopców, jest niezwykle istotna nie tylko ze względu na poważne powikłania, na które narażony jest pacjent, lecz także z uwagi na chorobę podstawową, która może mieć charakter śmiertelny. Z tego powodu dzieci dotknięte przedwczesnym pokwitaniem typu centralnego powinny w pierwszej kolejności zostać poddane badaniom neuroobrazowym. W niniejszej pracy przedstawiamy przypadek 9,5-letniego chłopca, który został skierowany do Centrum Medycznego Rasoul-e-Akram ze wzmożonym ciśnieniem śródczaszkowym, nudnościami i wymiotami oraz silnymi bólami głowy trwającymi od trzech miesięcy. Rozwój drugorzędowych cech płciowych rozpoczął się u pacjenta 2 lata wcześniej i został zbagatelizowany. Jądra, penis oraz owłosienie łonowe pacjenta znajdowały się w stadium rozwoju odpowiadającym czwartemu stopniowi skali Tannera. Stwierdzono podwyższony poziom LH oraz FSH. Badanie histopatologiczne potwierdziło obecność gwiaździaka włosowatokomórkowego o stopniu złośliwości G1. U pacjenta wykonano operację odbarczającą w trybie pilnym. Po zabiegu wdrożono chemioterapię. Po upływie 2 lat od operacji chłopiec nadal otrzymuje chemioterapię, osiągnął 154 cm wzrostu i przejawia oczywiste cechy dojrzałości płciowej. Prowadzenie właściwej edukacji rodzin oraz personelu medycznego może zapobiec zbyt późnemu rozpoznawaniu i wdrażaniu leczenia przedwczesnego pokwitania, tym samym ułatwiając pacjentom prowadzenie normalnego życia, dostosowanego do ich wieku i potrzeb społecznych.

Słowa kluczowe: pokwitanie, przedwczesne, typ centralny

INTRODUCTION

Precocious puberty (PP), more frequent in girls (Muir, 2006), is defined as evolving physical changes of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys, although the exact age may vary based on ethnicity or other factors (Carel *et al*., 2009). In Iran, the mean age of puberty in girls has been reported to be 10.14, and precocious puberty is defined as occurring before the age of 7.5 years (Moayeri and Oloomi, 2006), higher in rural areas and in lower-education families (Delavar and Hajian-Tilaki, 2008), and 9.7 years in boys (Razzaghi Azar *et al*., 2006). Regarding the involvement of the hypothalamic-pituitary-gonadal axis, PP may be classified as central PP (CPP), arising from central nervous system (CNS) or peripheral PP (PPP) (Carel and Léger, 2008). CPP is mostly idiopathic in girls, but in more than half of boys an identifiable aetiology, commonly a space-occupying lesion (Ducharme and Collu, 1982), can be detected (Klein, 1999). Some studies have also described secondary aetiologies, such as high doses of radiation following brain tumours, trauma, infection, or an underlying disease like neurofibromatosis (Gleeson and Shalet, 2004).

Therefore, brain study, alongside hormonal assessment, is essential in each CPP case, especially in boys. On the other hand, CPP may be related to various origins (Bierich, 1975), which highlights the need for precise evaluations.

Here, we present the case of a 9.5-year-old boy with CPP originating from midline low-grade astrocytoma involving hypothalamus, who was presented to us with nausea and vomiting of three months.

CASE REPORT

The patient was a 9.5-year-old boy from one of the northeast rural areas of Iran, who was referred to Hazrat Rasoule-Akram Hospital in November 2013. He was the eighth child of the family, born full-term with no complications, by vaginal delivery. His birth weight and height were within normal range. He had no underlying disease, family history of brain tumours, or any endocrine disease. The development of secondary sexual changes, which had begun two years earlier, was treated herbally.

On admission, he had nausea/vomiting and severe headaches which had started three months earlier, and was developing losses of consciousness. He had no history of blindness or sensational disorders, or any history of seizures or dyslexia. His height at the time was 145 cm (z-score of 1.3 and 90.8% of percentile), and he weighed 40 kg (90% of percentile). He had a deep voice and was moody.

In physical examination, he revealed hyperpigmented skin and intact cranial nerves, but signs of increased intracranial pressure were detected in fundoscopy of the optic disc. His testes, penis, and pubic hair were at the fourth Tanner stage, with more than 4cc testicular volume (Fig. 1).

Paraclinical assessments showed bone age matching 14 years of age, and high basal values of luteinizing hormone (LH) and follicle stimulating hormone (FSH). All important serum tests are demonstrated in Tab. 1. Other serum parameters were within normal range. The magnetic resonance imaging (MRI) of the brain revealed a huge suprasellar mass extending to the third ventricle, that was hypointense in T1WI and hyperintense in T2WI, with bright enhancement (45 × 33 × 35 mm) (Fig. 2 A).

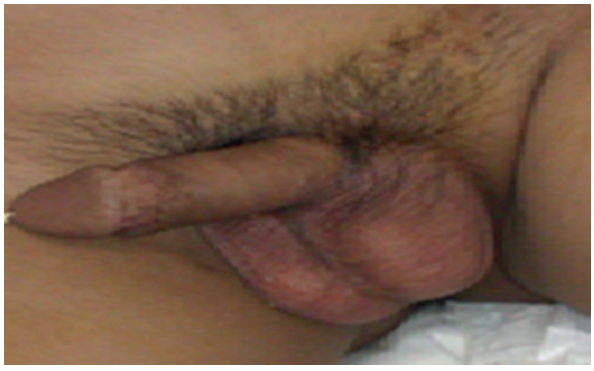

Fig. 1. The maturation of the patient's genitalia

Serum test	Unit	Patient's value	Normal range
Luteinizing hormone (LH)	mIU/ml	4.2	LH adult <7, pubertal age <0.4
Follicle stimulating hormone (FSH)	mIU/ml	6.0	FSH adult 3–20, pubertal age <2
Testosterone	ng/dl	460	Testosterone adult male: 270–1070, in 9–11 years <7–130
Prolactin	ng/ml	12	Prolactin <24
Human chorionic gonadotropin (βHCG)	mIU/ml	<10	βHCG <5
Thyroid stimulating hormone	μIU/ml	0.5	TSH 0.4–4

Tab. 1. Important hormonal serum tests of the patient

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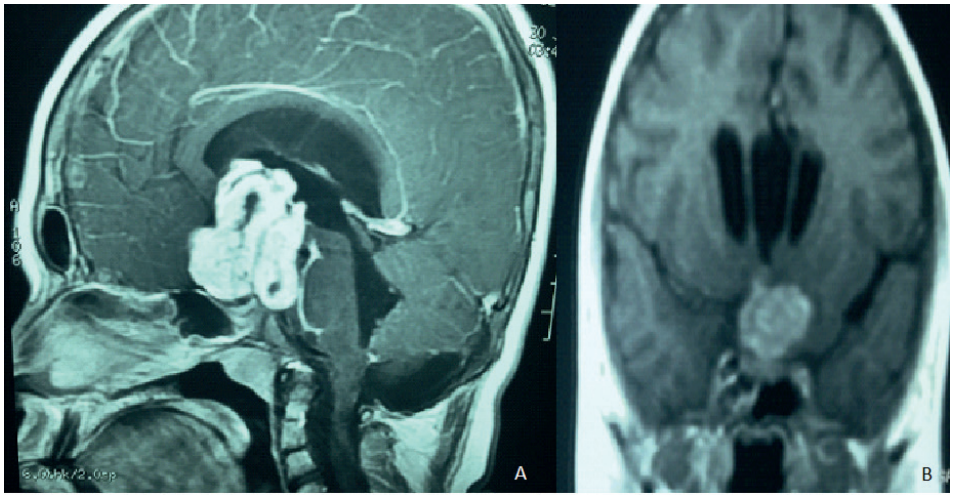

Fig. 2. Magnetic resonance imaging (MRI) findings of the patient. Fig. A represents the pre-operation imaging (a huge suprasellar mass extending to the third ventricle, hypointense in T1WI and hyperintense in T2WI with bright enhancement (45 × 33 × 35 mm), and Fig. B demonstrates the postoperation imaging (suprasellar mass with less enhancement, of 13 × 20 × 15 mm)

Emergency brain surgery was conducted: after right side pterional craniotomy and trans-sylvian approach to the suprasellar region, a hypothalamic-chiasmal mass appeared and was partially removed, and chemotherapy was started postoperatively. The chemotherapy included 6 courses, at 6-week intervals, consisting of vincristine (VCR), lomustine (CCNU), and procarbazine.

The pathologic evaluation confirmed low-grade pilocytic astrocytoma WHO grade 1; macroscopic result showed suprasellar intraventricular tumour, consisting of multiple pieces of brown soft tissue measuring 3 × 3 × 1 cm and 6 gr in weight, S.O.S:M/3, E:100%, and microscopic evaluation confirmed biphasic neoplastic tissue with hyper and hypocellular zones revealing cells with slightly pleomorphic and enlarged nuclei in fibrillary background. Scattered eosinophilic granular body was seen. Also, foci of haemorrhage were noted (Fig. 3). Post-op MRI revealed suprasellar mass with less enhancement (13 × 20 × 15 mm) (Fig. 2 B).

Gonadotropin-releasing hormone (GnRH) agonist (Diferelin) 3.75 mg was administered to the patient every 28 days; nevertheless, the patient showed no compliance for hormone therapy, and as a result of economic problems, did not continue hormonal medication. Two years after follow-up, the patient has matured genitalia, bone age matching 18 years, and a height of 154 cm.

DISCUSSION

In the present case report, the 9.5-year-old child was at Tanner stage 4, although Iranian studies have reported the mean age of the fourth Tanner stage to be 13.9 for boys (Razzaghi Azar *et al.*, 2006).

In this case, the patient was referred very late to a physician, with PP progress already neglected for two years, which resulted in his mature sexual and bone age. Therefore, hormonal therapy would not have helped him greatly anyway, yet he failed to complete it.

As PP affects the child's final height, and causes social difficulties for the patient, providing a thorough investigation on the details of this matter is critical for the sake of timely and proper diagnosis and treatment. Also, developing adequate knowledge concerning puberty is important for the entire healthcare system and society, so that primary prevention programmes related to sexual health education and adolescent mental health may be planned and executed (Ahmadi *et al.*, 2009).

Accordingly, paying sufficient attention to the examination of the genitals and assessment of sexual growth is essential for every child referred to a physician. The presented patient may have benefited more from treatment, had he been referred earlier.

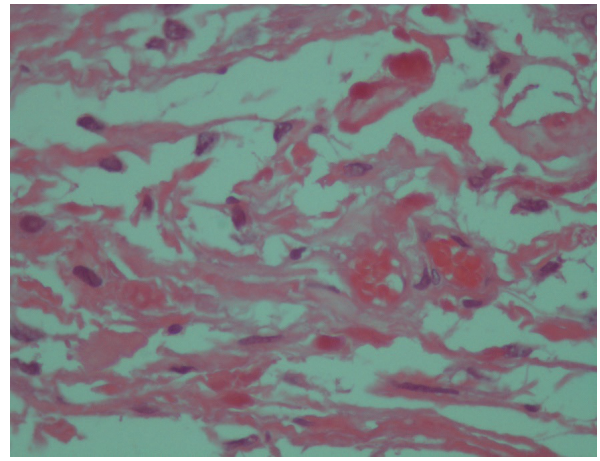

Fig. 3. Microscopic evaluation of the brain pathology: biphasic neoplastic tissue with hyper- and hypocellular zones revealing cells with slightly pleomorphic and enlarged nuclei in fibrillary background, with scattered eosinophilic granular body and foci of haemorrhage

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As other studies have indicated, pubertal age is closely related to race, yet few studies have evaluated boys' pubertal age in Iran. As Ahmadi *et al.* (2009) indicated, assessing puberty in boys is limited, as Iranian boys feel embarrassed to express or discuss their genital changes. Some other Iranian conveys have also specified the stressful complications the Iranian adolescents face during puberty (Golchin *et al.*, 2012; Koohestani *et al.*, 2009).

Early puberty, medically known as precocious puberty, has thus rarely been investigated in Iranian population. One case has been reported, of a 6.5-year-old boy referred for PP due to Leydig cell tumour of testis (Ghazi *et al.*, 2001), which is a type of peripheral PP. Spermatogenesis in males or ovulation in females appear only in CPP, and therefore adult-sized testicles can be noticed in this type only, as in the present case (Jolly, 1951).

Many studies have reported cases of CPP due to brain tumours. Hamartomas, teratomas, or ependymomas have been reported in many cases, and some state them to be the most common causes of CPP (Choi *et al.*, 2013). Some have even proposed classic triads for the diagnosis of hamartoma (Nebesio and Eugster, 2007).

Other pathologies, such as optic glioma, astrocytoma, chorioepitheliomas, or neurofibromas have also been proposed as possible aetiologies (Ducharme and Collu, 1982). However, the details have not been widely assessed. A similar Iranian case report has reported PP in a 3-year-old boy with remarkable failure to thrive and nystagmus, which was ultimately found to be due to hypothalamic pilocytic astrocytoma (Vakili *et al.*, 2004). He had high levels of LH and FSH, similar to the present case, but also high thyroid stimulating hormone (TSH). His case, however, was due to diencephalic syndrome, and all presentations were associated with radiation and tumour resection.

Some suggest that the involvement of posterior hypothalamus associated with an intact pituitary gland can be the single reason to induce PP (Jolly, 1951).

Some other studies have investigated more cases with longer follow-ups. Choi *et al.* (2013) studied 61 boys, and reported two cases of pilocytic astrocytoma. Jakubowska *et al.* (2011) followed 39 girls and 17 boys diagnosed with PP for 10 years, reporting 6 boys to reveal gonadotropin-dependent central puberty: 5 cases were idiopathic, and one had a brain tumour – astrocytoma. As it seems, the case presented is a rare phenomenon.

Thus, more studies need to be conducted in order to explain the cause, the best diagnostic criteria, specific treatment, or any accompanying syndromes regarding this rare brain tumor causing precocious puberty.

Primary CNS tumours in Iran have been reported to have an incidence of 2.74 per 100,000 person-years with a benign to malignant ratio of 1.07 (Jazayeri *et al.*, 2013). Another Iranian study has indicated 84% of all brain tumours to be meningioma (26%), followed by astrocytoma (23.4%), pituitary adenoma (14.2%), glioblastoma (5.1%), and ependymoma (4.8%), and has reported male predominance in astrocytoma tumours, with a ratio of 1.5 (Mehrazin *et al.*, 2006). A recent study in Northeast of Iran investigated 87 non-brainstem astrocytoma cases, and has reported the best treatment to be gross total resection with 100% survival rate for grade 1 (Anvari *et al.*, 2014), as in the presented case. A neuro-endocrinology meeting in Mashhad has also indicated resection as the most effective treatment (Anvari *et al.*, 2011). They have suggested temozolomide (TMZ) for treatment of most brain tumours, including astrocytoma. The patient in our case, however, responded to the chemotherapy regimen explained above.

We report this case with the intention to highlight the importance of educating medical staff and families in the appropriate diagnosis and treatment of this endocrine dysfunction which has a noticeable effect on the quality of life of the affected patients.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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