Case Report

Acromegaly in preadolescence: A case report of a 9-year-old boy with acromegaly

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ABSTRACT

Background: Acromegaly has been reported in adolescents and young adults, but it is unusual in preadolescence. Diagnosis and management pose different challenges in this age group. Here, we present a rare case of acromegaly in preadolescence.

Case Description: A 9-year-old boy presented with acromegalic features and MRI revealed a pituitary tumor. He was diagnosed as having growth hormone secreting pituitary adenoma based on the multidisciplinary assessment, and underwent gross total tumor resection through an endoscopic endonasal approach (EEA) with subsequent normalization of the hormonal parameters.

Conclusions: Advances in EEA have made safe removal and cure possible even in children. However, long-term follow-up is needed in such younger patients with multidisciplinary management by neurosurgeons, endocrinologists, pediatricians, and ENT surgeons.

Keywords: Acromegaly, Endoscopic endonasal approach, Growth hormone secreting pituitary adenoma, Preadolescence

INTRODUCTION

Pituitary adenomas are uncommon in childhood accounting for about 2.5% of supratenitorial tumors in children. Somatotropinomas are even rarer. By definition, acromegaly is a disease of adulthood occurring after closure of the epiphyseal growth plate, whereas gigantism manifests before epiphyseal fusion. Here, we present a rare case of acromegaly in a preadolescent boy along with discussions on some of the helpful diagnostic indicators and recent advances in management.

CASE PRESENTATION

History and examination

A 9-year-old boy presented with acromegalic features and rapid height growth discovered 4 months before presentation during school physical examination. He had complained of intermittent
headache and had a recent history of snoring during sleep. The parents and siblings had normal height and physical features with no history of endocrinopathies. On examination, he had a height of 151.8 cm (more than 2SD for age), weight of 40.2 kg, and hypertrophy of the lips. The patient had a shoe size of 24.5 cm (corresponding to the size appropriate for a Japanese boy of about 15 years old). The patient’s visual assessment was normal. Examinations of the cardiovascular and other systems yielded essentially normal results.

**Laboratory and radiological diagnosis**

Hormonal assay showed marked elevation of the levels of growth hormone (GH) and insulin-like growth factor (IGF-1). Random GH was 25.0 ng/ml, IGF-1 was 873 (99–423 ng/ml), with nadir GH during 75-g oral glucose tolerance test (75 g OGTT) of 15.9 ng/ml. Apart from the moderate increase in free T3 (5.27 pg/ml), other pituitary hormones were within the normal limits. Magnetic resonance imaging (MRI) of the brain revealed a pituitary tumor measuring 12 × 10 × 9 mm, without cavernous sinus invasion [Figure 1a and b]. Radiography of the skull and extremities showed prominence of the jaw and cauliflower appearance of the hands [Figure 1c and d].

**Treatment and postoperative course**

A preoperative diagnosis of GH-secreting macroadenoma was made, and tumor resection was performed through an endoscopic endonasal approach (EEA). Although the working space during the nasal and sphenoid phase was very narrow due to the preadolescent age and acromegalic features, it was possible to manipulate surgical instruments smoothly during sellar phase. The tumor was whitish and soft, and internal debulking was done using a double-suction technique. The pseudocapsule was also removed, and finally gross total resection of the tumor was performed [Figure 2a-d]. Intra- and postoperative courses were uneventful. The GH reduced to 0.9 ng/ml on postoperative day 6, with normalized IGF-1 (402 ng/ml) in the following week, and postoperative imaging showed satisfactory tumor resection [Figure 1b]. However, nadir GH level during 75 g OGTT remained insufficient with suppression of 1.3 ng/ml. Histopathological diagnosis was confirmed as GH secreting pituitary adenoma [Figure 3a-c]. The results of genetic testing were negative for genetic diseases, including McCune-Albright syndrome. He has been followed-up by neurosurgeons and pediatricians with brain imaging and biochemical assay every 6 months for 2 years, and no recurrence was confirmed.

**DISCUSSION**

Acromegaly is relatively rare with an incidence ranging from 3 to 11 per 1 million persons/year, and a prevalence of about 60/million. It is particularly uncommon in childhood, with features developing insidiously over decades, and many authors have reported a median age of diagnosis above 40 years with an estimated delay of 5–with an estimated delay of 5 years childhood, with many reports on acromegaly in adolescents and young adults, but few reports in preadolescents due to its rarity in this age group. [2,17]
However, most of the clinical manifestations are insidious and in this age group, usually go unnoticed or under recognized by close relatives and even caregivers. Some are misrepresented as normal growth and developmental changes, for example, the dramatic increase in shoe size and rapid height increase in the present case. Other subtle symptoms, such as headache and mild visual disturbances arising from tumor mass effect, may also be dismissed at the early stages until they become prolonged and debilitating.

The role of anthropometric measurements in making a diagnosis of acromegaly in preadolescence has yet to be determined. Measurements, such as the heel pad thickness, ring size, lean body mass, fat mass, and bone mineral density, may be difficult to interpret and apply uniformly across the different age groups in the preadolescent stage. Whereas there are standardized cutoff points in the adult population, these cannot be accurately extrapolated and adapted for management in this younger population. For example, the 9-year-old boy described here had a heel pad measurement of 18.5 mm, which may be quite significant for his age but fell far below the adult cutoff of 21 mm, thus making it appear clinically insignificant. It is believed that serial increments in the parameters of a particular child expressed as velocity increase may be more helpful in diagnosing acromegaly in this population than simply using cut-off points. In addition to clinical assessment, biochemical analysis and brain imaging contribute to making a diagnosis of acromegaly and confirming the presence of pituitary adenoma or hyperplasia. Hormonal assay is crucial for the diagnosis. The accuracy of random GH measurements in making a diagnosis of acromegaly has generally been questioned considering the pulsatile nature of GH secretion and its sensitivity to sleep. This is an even greater concern in children due to the additional changes in GH levels according to age. Whereas the use of random GH in routine clinical practice in adults has been validated by a number of studies in which good correlations between random GH measurements and the nadir GH measurement during 75 g OGTT were demonstrated, this cannot be done with certainty in children. This is because, to the best of our knowledge, there have been no such studies to corroborate these findings in preadolescents bearing in mind the influence of age on GH secretion. Therefore, as it is difficult to determine the hormonal condition after surgery, the patient is being closely observed and the option of medical therapy is not being considered at present as his clinical state has remained stable according to endocrinological pediatricians.

Occurring after fusion of the growth plates, individuals with acromegaly usually manifest with thickened bones of the jaw and extremities as well as hypertrophy of soft tissues giving the characteristic features of the disease, including coarse facial appearance, broadened nose, large hands and feet, obesity, organomegaly, hyperhidrosis, and snoring, the latter of which may be an early manifestation of obstructive sleep apnea. The present patient was positive for most of these features despite his preadolescent age. In considering acromegaly in this patient, it is important to consider the recent onset of snoring, rapid acral enlargement as evidenced by the significant increase in his shoe size, and recent enlargement of his lips and nasal wings. Nagata et al. reviewed GH-secreting pituitary adenomas in childhood and young adults and reported that no preadolescent patients had acromegalic features. The present case report showing the possibility of developing acromegaly even in preadolescence, not gigantism, is therefore clinically valuable.

Clinical suspicion is a critical factor in making a diagnosis of acromegaly in childhood. However, most of the clinical manifestations are insidious and in this age group, usually go unnoticed or under recognized by close relatives and even caregivers. Some are misrepresented as normal growth and developmental changes, for example, the dramatic increase in shoe size and rapid height increase in the present case. Other subtle symptoms, such as headache and mild visual disturbances arising from tumor mass effect, may also be dismissed at the early stages until they become prolonged and debilitating.

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Genetic screening for markers of familial acromegaly is also an important aspect of management of acromegaly in preadolescence. About half of the cases of pituitary gigantism and acromegaly in young adults occur in the context of an identifiable germline or somatic mutation. The goals of treatment for acromegaly in children are amelioration of clinical signs and symptoms, prevention of comorbidities, and normalization of life expectancy as in adult patients. The therapeutic options include surgery, medical therapy, and radiotherapy. Historically, hormonal treatment with testosterone or stilboestrol has been attempted in children but largely abandoned due to poor outcomes. Conventional microscopic transphenoidal surgery, although the first-line treatment for GH-secreting pituitary adenomas, is technically difficult in children who have smaller, less developed nares. In addition, the

Figure 3: Histopathological photographs. The tumor was composed of monomorphic neoplastic cells with eosinophilic cytoplasm (H and E, ×100) (a). Most of the neoplastic cells showed immunoreactivity for GH in their cytoplasm (immunohistochemistry, ×100) (b). The Ki-67 proliferation index was 3% (22/725) (immunohistochemistry, ×100) (c).
sphenoid sinus is present as small cavities at birth, with pneumatization being uncommon before the age of 12 years. The conchal type in which there is a thick bone separating the sella from the sphenoid sinus, is the most common type in the preadolescent age. This makes intraoperative identification of the sella floor challenging, as well as gaining access through it, all of which may contribute to a higher complication and lower overall surgical remission rate in children compared with adults. However, with recent advances in EEA, the use of high resolution endoscopes, intraoperative neuronavigation, and high-speed drills these difficulties were surmounted in the index case, achieving complete resection with minimal or no complications. On the other hand, postoperative nasal discomfort due to manipulation of the nasal mucosa in the narrow nasal cavity has not been resolved. ENT surgeons can play an important role in postoperative management in the nose.

In preadolescence, medical therapy with somatostatin analogs, GH receptor antagonists, and dopamine agonists are reserved only for cases with uncontrollable disease after surgery. Pegvisomant, a GH-receptor antagonist, showed some promise in children in a small study, decreasing the serum IGF-1 levels with complete resolution of acromegalic features in all three children studied even when surgery, octreotide, and cabergoline had previously failed to produce satisfactory results.

Radiotherapy carries a significant risk in the preadolescent population as it may result in panhypopituitarism with severe consequences for normal growth and development. Taking the delayed action of radiotherapy into consideration in addition to the complications arising from its use, it is rarely recommended in this population.

The present patient has maintained normal random GH and IGF-1 levels after surgery, although his nadir GH in 75 g OGGT level showed a decrease from the preoperative level and has still not reached hormonal remission according to the adult criteria. Therapeutic efficacy is assessed using various indices and long-term follow-up should be adopted in this population, as the risk of recurrence may be slightly higher than in adults. Serum GH and IGF-1 levels should be monitored with annual pituitary MRI studies. It is essential to care for acromegaly in the preadolescent stage by assessment, diagnosis, treatment, and follow-up through a multidisciplinary approach by neurosurgeons, endocrinologists, pediatricians, and ENT surgeons.

CONCLUSIONS
This case illustrated the importance of high clinical suspicion in making a diagnosis of acromegaly even in younger patients. It is difficult, however, to achieve cure by resection through the EEA in preadolescent patients. Genetic testing and long-term follow-up with multidisciplinary management are recommended in such young patients.

Ethical approval
All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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