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A PATIENT WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 PRESENTED WITH PRECOCIOUS PUBERTY

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ABSTRACT

Multiple Endocrine Neoplasia Type 1 (MEN1) is an autosomal dominant inherited tumour syndrome. Mean age at onset of MEN1 is rare before and during puberty. Although there are two case reports about MEN1 and delay puberty, early and rapidly progressive puberty with MEN1 has no reported. We presented a case whose father has MEN1, applied with central precocious puberty. In pituitary MRI, hypointense region which was stabil in size during the follow up, was seen in intermediate lob but it was not interpreted in favor of the adenoma. On admission, serum calcium level was high whereas serum phosphorus, parathormone levels were normal. In follow up, PTH increased, and patient was diagnosed as MEN1. The diagnosis confirmed by moleculer analysis. This case emphasize relevance of early screening of endocrine disorders in members of families with MEN1. Precocious puberty can also be detected in the follow up of patients with MEN1.

Introduction

Multiple Endocrine Neoplasia Type 1 (MEN1) is an autosomally transmitted hyperplastic or neoplastic disorders of some endocrine and non-endocrine organs (1). The gene causing MEN1 is located on the long arm of chromosome 11 (11q13) and is a known tumor suppressor gene that encodes a 610 amino acid protein called menin (2). MEN syndromes are rare cancer syndromes that occasionally present in childhood (2). In general, patients seen in the pediatric setting have dominantly inherited forms of the disease diagnosed in the preclinical state through prospective genetic testing (2). Sporadic and atypical forms also occur, and the presentation of endocrine neoplasia in childhood should always prompt consideration of an inherited genetic condition, as there may be important implications for long-term surveillance of the patient and other family members (2). Patients with MEN1 mostly develop parathyroid (95%), pancreatic (40%), and pituitary (30-40%) tumours (1,3). Mean age at onset of MEN1 associated pituitary tumors is the 4th decade (2). Although it is very rare before and during puberty, pediatric patients as young as 5 years of age have been reported (2,5-8). MEN1-associated anterior pituitary tumors most commonly secrete prolactin (60%), followed by tumors that secrete growth hormone (25%). Less than 5% secrete corticotropin and others are non-functional (3). Compared with non-MEN1 pituitary tumors, MEN1 pituitary tumors tend to be larger (macroadenomas) and more aggressive, with a higher rate of infiltration of tumor cells into normal pituitary tissue (4). In this article, we described an unusual presentation of MEN 1 syndrome that is open to interpretation for being coincidence or alarming sign of syndrome. Although there are two case reports about MEN1 and delay puberty (5,8), to our knowledge, early and rapidly progressive puberty with MEN1 has not been reported except our case.

Case

Eight year and 5 month old girl whose father has MEN1, applied with pubic and axillary hair that were detected 10 months ago. At that time, her Tanner stage was 2. The patient was diagnosed as central precocious puberty as a result of LHRH test (Table 1). Bone age was advanced (2.5 years more than chronological age). Her predicted adult height was calculated considerably shorter than her target height and Gonadotropin hormone-releasing hormone (GnRH) analogue treatment was given to patient. In pituitary Magnetic Resonance Imaging (MRI), hypointense region which was stable in size during the follow up, was seen in intermediate lob but it was not interpreted in favor of the adenoma. The biochemical tests durning diagnosis of MEN1 were given in Table 2. At admission serum calcium level was high whereas serum phosphorus, parathormone (PTH) and 25-hydroxyvitamin D (25-OH vit D) levels were normal. PTH increased and hyperparathyroidism was detected during follow up. The ultrasonography (USG) also showed adenomas in parathyroid gland and patient was also diagnosed as MEN1 same as her father. Two parathyroid adenomas with diameter 3.6 mm and 5.9 mm respectively were detected by USG. Familial pedigree is given in Figure 1. Her father (case 3 in figure) has a heterozygous mutation c.1699_1671delinsC in the exon 10 of MEN1 gene. The molecular analysis of our case also showed the same pathological variant in MEN1 gene as her father. Since growth velocity decreased during the GnRH analogue treatment, growth hormone (GH) treatment was also started to contribute the final adult height. GH stimulation tests were normal. The last assessment was done at 11 year and 9 month old. The GnRH analogue treatment was stopped where the GH treatment had been continued for 8 months more according to the bone age. The serum calcium levels were between 10.4 to 10.9 whereas PTH levels slightly increased during the follow-up. Urine calcium/creatinin was normal. In abdominal USG, nephrolithiasis had not been observed and pancreas, surrenal glands were also detected normal. Other pituitary hormones, blood glucose remained in the normal range. She has not needed any medical treatment for hypercalsemia. The hypointense region in pituitary MRI has been stable during the yearly control MRIs in 4 years.

DISCUSSION

In this article, we described the clinical presentation and 4 years follow-up of a pediatric case of MEN1 syndrome. Previous reports state that the average age at diagnosis of MEN1 in sporadic cases or a proband is 47.2 ± 15.3 years, whereas a family history results in diagnosis about 10 years earlier (9). For diagnosis, the guideline state that the occurrence of one of the MEN1-associated tumors in a first-degree relative of a patient with a clinical diagnosis of MEN can be accepted (3). As our patient presented with central precocious puberty followed by hypercalcemia and hyperparathyroidism, her clinical diagnosis was confirmed by subsequent genetic testing because of family history. Clinical practice guidelines have been developed for the surveillance and screening for MEN1-associated tumors including clinical, biochemical, and imaging data starting in MEN1 mutation carriers as early as 5 years of age (2,3). Recommended age to start screening for parathyroid is 8 whereas for pituitary is 5. Similar to reported guidelines, our patient demostrated hypercalcemia at the admision for precocious puberty on 8 years and 5 month old, however meaningful high PTH was seen after persistent hypercalcemia during the follow-up. On the other hand, recommended annual biochemical screening for pituitary is mentioned in literature [prolactin (PRL) and insulin-like growth factor-1 (IGF-1)], but the frequency of clinical follow-up of these children's growth chart or pubertal signs are missing. moreover, there is still considerable variability in the recommendations from other endocrine and oncologic societies (10). So, while the

principles of screening other possible including endocrine organs are well known in MEN1 syndrome (3), questions may remain regarding the type, quantity, time and frequency of screening in children who have family history (2,10,11). We want to point the importance of early clinical follow-up of children in MEN1 families with this case, and discuss the possible different clinical endocrinologic presentations. The goal of screening is to identify endocrine tumors at an early stage where interventions could reduce morbidity and mortality from malignant transformation (2,3,10). Screening may also serve to reassure MEN1 mutation carriers that they have not yet developed tumors (2,3,10). However, early clinical follow-up is necessary not only for detecting tumors early, but also for early diagnosis of growth or pubertal disorders which may be the first sign of the syndrome or may cause other undesired endocrinologic problems. Although the question of etiology of precocious puberty remain unanswered in our case, we want to present this patient because of no case report with early and rapidly progressive puberty in MEN1.

Evaluation for patients with hyperparathyroidism typically includes an ultrasound as an initial screening for underlying parathyroid adenoma followed by nuclear technetium Tc-99m sestamibi scintigraphy for confirmation. Sestamibi scintigraphy has a sensitivity and specificity of >90% for lesions that demonstrate retention of sestamibi radiotracer on delayed imaging (12). According to results of case and confirmation the diagnosis with molecular analysis, sestamibi scintigraphy was not performed.

The serum calcium levels were stabil during the 4 years follow-up. Although her PTH levels slightly increased by years, she had no serious hypercalcemia or any complications including nephrocalcinosis, osteopenia, osteoporosis or fractures. However, there is one more question that come to fore; which criteria needed or what should be the best age for parathyroidectomy?. We also want to draw attention to this question with this case presentation.

CONCLUSION

This case emphasize relevance of early screening of endocrine disorders for members of families with MEN1 because of diversity of endocrine disorders. It should be kept in mind that rare endocrine presentations as precocious puberty can also be detected in the follow up of patients with MEN1. Although it is a rare syndrome, an understanding of the approach to a child with a genetic diagnosis of MEN is important, as regular clinical follow-up or surveillance for associated tumours should facilitate early diagnosis and treatment of both tumors and associated other endocrinologic problems, thereby improving long-term morbidity and mortality.

Table 1. LHRH test results

LHRH Test	FSH (mIu/ml)	LH (mIu/ml)
0´	4.6	0.5
30´	10.3	5.6
60´	12	4.3
90´	12.5	2.2

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, LHRH: luteinizing hormone releasing hormone

Table 2. Biochemical results at diagnosis

Laboratory	
Glucose (mg/dL)	77
Ca (mg/dL)	10.7↑
P (mg/dL)	4.0
ALP (U/L)	284
PTH (pg/mL)	68.8↑
1-25 OH D3 (nmol/L)	117
25-OH D3 (pmol/L)	19.2
PRL (ng/dl)	5.7
Insulin (uIU/mL)	15.2
TSH (uIU/mL)	1.9
FT4 (ng/dL)	1.5
Cortisol (ug/dL)	9.8
ACTH (pg/mL)	5.2
IGF-1 (ng/mL)	780
IGFBP3 (ug/mL)	3.6

ACTH: Adrenocorticotropic hormone, ALP: Alkaline phosphatase, Ca: Calcium, FT4: Free thyroxine, IGF-1: Insulin-like growth factor I, IGFBP3: Insulin-like growth factor-binding protein 3, P: Phosphorus, PRL: Prolactin, PTH: Parathormone, TSH: Thyrotrophin-Stimulating Hormone, 1-25-OH D3: 1-25-hydroxyvitamin D, 25-OH D3: 25-hydroxyvitamin D

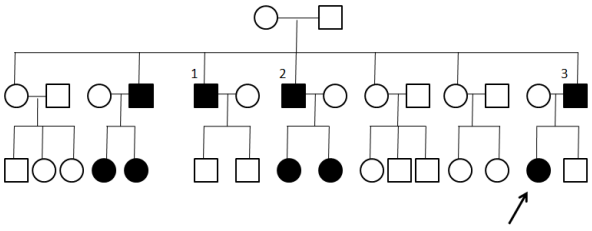

Figure 1. Familial pedigree (Patient 1,2, and 3 had total parathyroidectomy)

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