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ORIGINAL ARTICLE

MEN1 in children and adolescents: Data from patients of a regional referral center for hereditary endocrine tumors

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Abstract
Purpose To retrospectively evaluate the age of onset of MEN1-associated lesions in a group of affected children and adolescents and to compare the clinical features of our series with the evidence derived from the literature.
Methods The study population consisted of 22 Italian children and adolescents (age 6–31 years at the time of the inclusion in this study) all with a clinical and/or a genetic diagnosis of MEN1 performed before the age of 16 who have been followed-up regularly from 1998 to 2016 at the Regional Referral Center for Hereditary Endocrine Tumors. Clinical, biochemical, imaging and genetic data have been collected for each patient.
Results Ten subjects (45.5%) have not yet presented any clinical/biochemical/radiological manifestation of MEN1 disease, whereas 12 patients (54.5%) developed at least one MEN1-associated endocrine manifestation. The second group of patients was significantly older than the first one. The most frequent manifestation was primary hyperparathyroidism (50%), followed by pituitary tumors (prolactinomas) (31.8%) and nonfunctioning pancreatic neuroendocrine tumors (9%). The earliest cases of primary hyperparathyroidism and prolactinoma were a 12-year-old girl and a 13-year-old boy, respectively.
Conclusions MEN1 disease seems to present with different features in children and adolescents from those in adults. Our study confirms the fundamental importance of screening for tumors in young MEN1 patients beginning in early childhood, in order to avoid diagnostic and therapeutic delays.

Keywords Multiple endocrine neoplasia type 1 · Clinical diagnosis · Genetic diagnosis · Children and adolescents · Early onset · Disease screening

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant inherited multiple endocrine tumor syndrome, mainly affecting parathyroid glands, gastro-entero-pancreatic neuroendocrine tissues, and anterior pituitary [1].

In children and adolescents, the MEN1 diagnosis is principally made by the genetic screening of the *MEN1* gene, within a pedigree with a previously identified *MEN1* mutation.

Penetrance of *MEN1* mutations is age-dependent; however, although it appears to be almost negligible before 5 years of age, clinical manifestations of MEN1 have occurred in some patients by the age of 5 years. Therefore, Clinical Guidelines suggest the performance of genetic testing in asymptomatic relatives of MEN1 mutated patients as soon as possible, certainly within the first decade of life, hopefully before 5 years of age [2].

Genetic testing presents numerous advantages: it requires only a single blood sample, it can be performed at any age and, in theory, it does not need to be repeated during life. A negative genetic result allows us to avoid further MEN1 clinical surveillance in those subjects. It is fundamental to regularly monitor all patients at high risk of developing

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MEN1-associated tumors (index cases and germline mutated *MEN1* carriers) using a specific screening program, in order to promptly diagnose tumors throughout life without any delay.

Screening should start during early childhood [3] and continue throughout life, as the first clinical manifestations can arise even during the eighth decade of life in some patients [2]. Table 1 shows the age of initiation and modalities of screening for each of the main MEN1-associated tumors according to the latest MEN1 Guidelines; respective levels of clinical evidence are also indicated [2].

The aim of our retrospective study is to evaluate the age of onset of MEN1-associated lesions in a group of affected Italian children and adolescents and to compare the clinical features of our series with evidence on MEN1 in young patients derived from literature.

Subjects and methods

The study population consists of 22 Italian children and adolescents, aged from 6 to 31 years at the time of the enrollment in the present study, all with a clinical and/or genetic diagnosis of MEN1. All patients were regularly followed-up at the Regional Referral Center for Hereditary Endocrine Tumors of the Endocrine Unit in the Department of Surgery and Translational Medicine, University Hospital Careggi in Florence from 1998 to 2016. A total of 160 MEN1 patients (55 males and 105 females) were referred to our Center and regularly evaluated during the same period of time. The study was approved by the local ethics committee of Careggi Hospital, and informed consent has been obtained from all legal guardians of our minor patients.

Patients were annually tested for parathyroid hormone (PTH) and calcemia, prolactin (PRL), insulin-like growth factor 1 (IGF-1), growth-hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), gonadotropins, glycaemia, plasma insulin, C-peptide, serum gastrin, plasma vasoactive intestinal peptide (VIP), pancreatic polypeptide (PP), glucagon, and chromogranin-A (CgA). Secretin provocative test was performed every 12–18 months beginning at the age of 15. Adrenal function was evaluated in case of clinical manifestations. Imaging tests were performed in the presence of biochemical alterations and/or clinical signs and symptoms. Particularly, abdominal computed tomography (CT)/magnetic resonance imaging (MRI) were performed every 2–3 years; if scintigraphy with somatostatin analogous was positive in presence of gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), it was repeated every 2 years.

Clinical, biochemical, imaging and genetic data were collected and recorded in a specific database in association

Table 1 Diagnostic screening of MEN1-associated tumors according to the latest MEN1 guidelines

Men1-associated disease	Age of initiation (years)	Laboratory parameters	Level of clinical evidence	Imaging test	Level of clinical evidence
Primary hyperparathyroidism	8	Plasma calcium and PTH (annually)	Strong recommendation; high quality	–	–
Anterior pituitary tumors	5	Plasma PRL and IGF-1 (annually)	Weak recommendation; moderate quality	MRI every 3 years	Weak recommendation; low quality
Gastrinoma	20	Fasting serum gastrin (annually) (±gastric pH; diagnostic values < 2)	Weak recommendation; low quality	–	–
Insulinoma	5	Fasting plasma insulin and glucose (annually)	Weak recommendation; low quality	–	–
Other pancreatic NET (glucagonoma, VIPoma, nonfunctioning pancreatic NET)	<10	Plasma glucagon, VIP, PP, CgA (annually)	Weak recommendation; low quality	CT, MRI or EUS annually	Weak recommendation; low quality
*Bronchial and thymic carcinoid	15	None (no increase in plasma CgA levels has been observed)	Strong recommendation; high quality	Chest CT or MRI every 1–2 years	Weak recommendation; very low quality
Adrenal tumors	<10	Only in case of suspected clinical manifestations and/or if the tumor size is >1 cm	Strong recommendation; moderate quality	Abdominal CT or MRI annually with pancreatic imaging	Weak recommendation; low quality

Notes: *screening should be performed even after prophylactic thymectomy

NET neuroendocrine tumor, *PTH* parathyroid hormone, *PRL* prolactin, *IGF-1* insulin-like growth factor-1, *VIP* vasoactive intestinal peptide, *PP* pancreatic polypeptide, *CgA* chromogranin-A, *CT* computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasound, *cm* centimeter

with a specific, unique anonymous alphanumeric code to assure the privacy of the patient, and each patient was referred to in the study only by this identifying code. Data collected in the database included: birth date, gender, age at genetic diagnosis (date of genetic test), *MEN1* gene mutation, first MEN1 manifestation, age at clinical diagnosis (date of the first clinical manifestation, defined as the MEN1-associated lesion that was firstly discovered), MEN1-associated endocrine manifestations, other comorbidities, MEN1-related surgical history and pharmacological treatments.

Data included in the database are presented as percentages, means and standard deviations and medians (range).

The comparison between the median age of MEN1 patients with and without at least one endocrine manifestation of the disease was performed by Mann–Whitney *U*-test. A p-value < 0.05 was considered as the level of statistical significance.

Twenty-one patients underwent the *MEN1* genetic test after a first degree relative was diagnosed with a *MEN1* mutation; each was tested for the specific pedigree-associated mutation by a PCR-based Sanger sequencing of the specific mutation-containing exon or intron-exon junction of the *MEN1* gene. One patient was a proband; he underwent *MEN1* mutational analysis before all his family members.

Results

Clinical, genetic, and therapeutic features of our series of young MEN1 patients are summarized in Table 2.

A genetic and/or clinical diagnosis of MEN1 syndrome was performed in all 22 subjects before the age of 16: 10 females (45.5%) and 12 males (54.5%). The cases were familial, belonging to 14 different MEN1 pedigrees, and a *MEN1* mutation was identified in all cases. Only one patient (case 4, Table 2) was a proband presenting the same age of both genetic and clinical diagnosis, whose family has been subsequently screened for *MEN1* mutation. All other cases were family members identified as MEN1 first via genetic screening. The mean age at genetic diagnosis of MEN1 was 9.4 ± 3.75 years (range 0–14). The age at the genetic diagnosis of the proband (case 4, Table 2) was 13 years, whereas the age at MEN1 diagnosis of his brother and sister was 7 and 10, respectively.

Genetic analysis confirmed the absence of mutational hot spots in the *MEN1* gene and mutations have been identified all along *MEN1* exons (except for exons 5, 6, and 7) and intron-exon junctions (Table 2). In our series of patients, we identified missense, nonsense, frameshift, and splicing site mutations. Two brothers harbored a double mutation on the same *MEN1* allele, not associated with a higher aggressiveness of the syndrome (cases 11 and 12, Table 2).

To date, 10 subjects (45.5%) [median age 12 years (range 6–16)] have not yet presented any clinical manifestation associated with MEN1 and no abnormalities in biochemical tests or evidence of the disease by imaging examinations were detected (referred to as "still asymptomatic" patients). Conversely, 12 patients (54.5%) [median age 22.5 years (range 12–31)] developed at least one MEN1-associated endocrine manifestation; in detail, 10 of these patients were clinically asymptomatic and were diagnosed by routine biochemical tests and/or imaging investigations, whereas only two were symptomatic, showing pituitary tumor-induced headache with visual disturbances and primary hyperparathyroidism (PHPT)-related kidney stones, respectively. A significant difference was found in the median value of age between these two patient groups (U-test $= 5.0$; $p < 0.001$). Particularly, patients with MEN1-associated lesions were significantly older than MEN1 patients without any clinical/biochemical/radiological manifestation of the syndrome.

The most frequent clinical phenotype was PHPT which was present in 11 patients (50%) [six females (54.5%) and five males (45.5%)] followed by pituitary tumors (seven cases; 31.8%) [four females (57.1%) and three males (42.9%)] and pancreatic NETs (pNETs) (two females; 9%). PHPT was the only manifestation of MEN1 in four cases, while it was associated with other lesions in seven cases.

PHPT was the first MEN1 manifestation in 7 out of 12 patients (58.3%) who had developed MEN1-associated clinical and/or biochemical and/or radiological abnormalities; it was symptomatic (presence of a history of kidney stones) in only one out of 11 patients with PHPT (9%). Asymptomatic PHPT patients (10/11, 91%) were diagnosed by biochemical tests. The earliest case of PHPT was an asymptomatic normocalcemic 12-year-old girl. Patients with low levels of vitamin D were treated with oral supplements to exclude cases of secondary hyperparathyroidism [4].

The patient with symptomatic PHPT underwent surgery and then received pharmacological therapy; five asymptomatic PHPT patients had normocalcemia that did not require therapy and have been monitored with annual calcemia and PTH measurements; the remaining five asymptomatic patients were surgically and/or pharmacologically treated because of hypercalcemia. Particularly, 2/5 patients (40%) underwent total parathyroidectomy with autograft in the non-dominant forearm, 1/5 (20%) subtotal parathyroidectomy, and 2/5 (40%) partial parathyroidectomy (removal of only the single enlarged gland). Three out of five patients who were surgically treated also underwent total thymectomy. Pharmacological treatment of PHPT with calcimimetics (cinacalcet) was performed as first line

Table 2 Main characteristics of our series of children and adolescent MEN1 patients

Code	Gender	Note	Date of birth (month/date/year)	Age at genetic diagnosis: Years, date of genetic test	*MEN1* gene mutation	Age at clinical diagnosis (first clinical manifestation)	Age at biochemical and/or instrumental imaging diagnosis	First MEN1-associated endocrine manifestation	MEN1-associated endocrine manifestations	Other comorbidities	MEN1-related surgical history	Pharmacological treatments
1	M		09/22/2000	12 08/03/2012	c.Cys354Phe, exon 8	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	None	None	None
2	F	First degree cousin of 3	04/08/1993	7 06/02/2000	g.fs1364delC, exon 9	Still asymptomatic	18	PRL	PRL, normocalcaemic PHPT	None	None	Cabergoline
3	F	First degree cousin of 2	04/02/1993	7 06/02/2000	g.fs1365delC, exon 9	Still asymptomatic	19	PRL	PRL	Low level of vitamin D	None	Cabergoline
4	M	Brother of 5 and 6	10/30/1988	13 04/05/2001	g.sp893 + 1 G > A, intron 4	13	13	Headache and visual disturbances	macroPRL, PHPT	MacroPRL-induced secondary hypogonadism and severe osteoporosis,, low level of vitamin D, first degree left side varicocele	Subtotal parathyroidectomy (ablation of three glands) and total thymectomy in 2013	Cinacalcet (from January 2010 to October 2013) Neridronate for osteoporosisTestosterone replacement for hypogonadismCabergolineCholecalciferol
5	F	Sister of 4 and 6	03/11/1991	10 04/05/2001	g.sp893 + 1 G > A, intron 4	Still asymptomatic	26	PHPT	PRL, PHPT, non-functioning pancreatic NET	None	None	CinacalcetSomatostatin analogous25-hydroxy-cholecalciferol Cabergoline Inhibitor of protonic pomp (when needed)
6	M	Brother of 4 and 5	12/20/1994	7 04/05/2001	g.sp893 + 1 G > A, intron 4	Still asymptomatic	17	Lipoma	Lipoma, normocalcaemic PHPT	Low level of vitamin D	Ablation of lipoma from left thigh in 2012	Cholecalciferol
7	F		09/30/1992	8 10/23/2000	g.fs359–362del4, exon 2	Still asymptomatic	14	PHPT	PRL, PHPT, non-functioning pancreatic NET, subcutaneous lipoma	None	Total parathyroidectomy with auto transplantation in the left forearm and total thymectomy in 2006	CholecalciferolCabergoline
8	M		04/12/1985	13 12/14/1998	c.Gly508Stop, exon 10	Still asymptomatic	15	PHPT	PHPT	Low level of vitamin D	Total parathyroidectomy with auto transplantation in the left forearm and total thymectomy in 2007	25-hydroxy-cholecalciferol
9	M		08/03/2005	At birth 08/05/2005	g.fs.1555insG, exon 10	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D	None	Cholecalciferol
10	F		04/29/1998	10 02/14/2008	g.sp1159 + 1 G > A, intron 7	Still asymptomatic	18	Normocalcaemic PHPT	Normocalcaemic PHPT	Low level of vitamin D	None	CholecalciferolCabergoline
11	M	Brother of 12	07/09/2004	4 12/23/2008	Double mutation on the same MEN1 allele (inherited from the mother):c-Leu249Pro, exon 4; g.fs1181delC, exon 8	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D	None	Cholecalciferol

Table 2 continued

Code	Gender	Note	Date of birth (month/ date/ year)	Age at genetic diagnosis: Years, date of genetic test	*MEN1* gene mutation	Age at clinical diagnosis (first clinical manifestation)	Age at biochemical and/or instrumental imaging diagnosis	First MEN1-associated endocrine manifestation	MEN1-associated endocrine manifestations	Other comorbidities	MEN1-related surgical history	Pharmacological treatments
12	M	Brother of 11	09/11/ 1998	10 12/23/ 2008	Double mutation on the same MEN1 allele (inherited from the mother):c-Leu249Pro, exon 4; g.fs1181delC, exon 8	Still asymptomatic	14	PRL	PRL, PHPT	Low level of vitamin D	Parathyroidectomy of one ectopic thoracic parathyroid gland in 2014	CholecalciferolCabergoline
13	F	Sister of 14	05/20/ 1996	14 10/25/ 2010	c.Val196Gly, exon 3	13	13	Renal colics	PHPT	Low level of vitamin D	Parathyroidectomy of one left parathyroid gland in 2010. Persistent PHPT post-surgery	CholecalciferolCinacalcet
14	M	Brother of 13	03/01/ 2001	10 08/30/ 2011	c.Val196Gly, exon 3	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D	None	Cholecalciferol
15	F		11/27/ 2006	6 06/29/ 2012	c.Gln450Stop, exon 9	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D	None	Cholecalciferol
16	M		10/07/ 2003	11 01/19/ 2015	c.Phe146Ser, exon 2	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D	None	Cholecalciferol
17	M		04/13/ 1999	15 01/23/ 2015	c.Asp148Asn, exon 9	Still asymptomatic	17	Normocalcaemic PHPT	MacroPRL, Normocalcaemic PHPT	Low level of vitamin D	None	Cabergoline
18	M	Brother of 19	04/08/ 2004	10 04/11/ 2014	g.fs317ins4, exon 2	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D, neonatal hypocalcaemia	None	Cholecalciferol
19	M	Brother of 18	05/20/ 2010	4 04/11/ 2014	g.fs317ins4, exon 2	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	None	None	None
20	F	Sister of 21 and 22	03/27/ 2004	12 03/04/ 2016	g.sp894–9G > A, intron 4	Still asymptomatic	12	Normocalcaemic PHPT	Normocalcaemic PHPT	Low level of vitamin D	None	25-hydroxy-cholecalciferol
21	F	Sister of 20 and 22	03/09/ 2006	10 05/18/ 2016	g.sp894–9G > A, intron 4	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D	None	25-hydroxy-cholecalciferol
22	F	Sister of 20 and 21	02/25/ 2002	14 05/18/ 2016	g.sp894–9G > A, intron 4	Still asymptomatic	Still asymptomatic	Still asymptomatic	Still asymptomatic	Low level of vitamin D	None	25-hydroxy-cholecalciferol

M male, *F* female, *PRL* prolactinoma, *PHPT* primary hyperparathyroidism, *NET* neuroendocrine tumor

therapy in 2/11 patients (18%). To date, cinacalcet is the current therapy in one patient (because she postponed surgery for personal reasons); another patient underwent parathyroidectomy after 3 years of pharmacological therapy; another, who was the only symptomatic patient, was treated with cinacalcet for persistent PHPT after parathyroidectomy. To date, all surgically and/or pharmacologically treated patients for PHPT show normocalcemia.

Pituitary tumors developed in seven patients [four females (57%) and three males (43%)]. In one case (14.3%) the pituitary tumor was the only manifestation of MEN1 disease, whereas it was associated with other lesions in six patients (85.7%).

Pituitary tumors were the first manifestation in 4 out of 12 MEN1 patients who showed at least one MEN1-induced clinical and/or laboratory and/or radiological alteration (33.3%). All pituitary tumors were prolactinomas, and five of them were clinically asymptomatic microadenomas. The remaining two prolactinomas were macroadenomas; they occurred in two young males (cases 4 and 17, Table 2). One of these two patients, who was a proband and represented the earliest case of prolactinoma in our series (13 years old), complained of headache and visual disturbances and had a macroprolactinoma-induced secondary hypogonadism, which led to a severe osteoporosis requiring pharmacological treatment with testosterone and neridronate (case 4, Table 2). The other patient (case 17, Table 2) was clinically asymptomatic. Prolactinomas were associated with a normal remaining pituitary function in all patients except the proband. Pharmacological approach with dopamine-agonists as first-line therapy was performed in all patients. This is their current therapy, which allows good control of the pituitary disease in all patients to date, except for those with macroprolactinoma who show hyperprolactinemia (case 4 and 17, Table 2).

Two females developed nonfunctioning pNETs, both revealed by CT. Both pNETs were associated with other MEN1-related lesions. One patient had two non-secreting lesions of 0.6 and 0.7 centimeters (cm) in size at the pancreatic head/body and body/tail crosses, respectively (case 7, Table 2); the other patient had a 1.3 cm lesion in the pancreatic tail, which secreted glucagon and scintigraphy with somatostatin analogous was positive, so pharmacological therapy with somatostatin analogous was performed as first-line therapy (case 5, Table 2). To date, neither pNET has been removed because they are stable in size at annual imaging follow-up. No cases of insulinoma, gastrinoma or other GEP-NETs occurred in our small series of MEN1 patients. Patients who underwent secretin provocative test showed a normal response.

Lipomas were present in two patients and, notably, this was the first clinical sign of MEN1 disease in one patient (case 6, Table 2).

To date, no other MEN1-associated lesions have manifested in our patients, particularly no cases of adrenal lesions or thymic NET have emerged.

Notably, neonatal hypocalcaemia occurred in one patient (case 18, Table 2), because his mother had hyperparathyroidism during pregnancy (MEN1 not yet diagnosed in the mother).

Discussion

MEN1 is a rare disease and the penetrance of *MEN1* mutations is known to be progressive during life [3]. This is confirmed in our study, which shows that patients with at least one manifestation of MEN1 syndrome are significantly older than those without any clinical/biochemical/radiological expression of the disease. Hence, large clinical studies in children with MEN1 are lacking and most of the current knowledge is related to MEN1 in adults.

Evidence of MEN1 in childhood mainly derives from case reports, but a retrospective study performed in a large group of 160 MEN1 patients (96 females and 64 males) under 21 years of age has recently been published by Goudet et al. [3]. At the time of the study, the age of 21 had been reached by 67% of patients, the age of 15 by 90%, the age of 10 by 97%, and the age of 5 by all patients. The study showed that the frequency of MEN1-associated tumors in children was quite different than adults: PHPT was the most frequent clinical manifestation also in children (75%), whereas, contrary to adults, pituitary adenomas were the second in frequency (34%), followed by GEP-NET (23%). These results are confirmed in our series, and they may be partly explained by different diagnostic approaches between young and adult MEN1 patients. Particularly, regular screening of MEN1 patients beginning in childhood allows prompt diagnosis of still asymptomatic tumors, whereas MEN1 diagnosis in adults might more often derive from tumor-associated clinical symptomatology.

Our study also showed that PHPT was the most frequent manifestation of onset in young MEN1 patients (58.3%), whereas prolactinoma was the second most frequent manifestation of MEN1 onset (33.3%). Similarly, Goudet et al. [3] showed that PHPT was the first laboratory and/or clinical manifestation of the syndrome in 56% of patients, while MEN1 onset was revealed by a pituitary adenoma in 21% of cases.

In agreement with Goudet et al. [3], PHPT was mainly asymptomatic in our series of MEN1 patients (10/11 patients; 91%), and only one young girl presented with symptomatic urolithiasis. All cases of PHPT occurred after 10 years of age in our study group, and this was partly in agreement with the study of Goudet et al. [3], in which 90% of PHPT cases occurred after 10 years, but the earliest

asymptomatic and symptomatic cases were a 4-year-old boy and an 8-year-old girl, respectively [3].

One single case of a severe complication of MEN1-associated PHPT is reported in literature: a MEN1 boy experiencing a PHPT-related ischemic stroke, in absence of hypertension, at the age of 14 [5].

Thirteen clinical cases (cases 1 to 13) of children and adolescents with MEN1-related pituitary disease derived from literature are summarized in Table 3.

MEN1-associated pituitary adenomas are known to be more frequent in females [2], with a 3.2/1 female/male ratio during the pediatric age, although macroadenomas appear to be more frequent in young males than in young females [3], and a greater aggressiveness of pituitary tumors in young males rather than in young females seems to arise from current evidence [3, 6–9] (cases 1–4, Table 3). Results from our series appear to confirm this aspect, as patients with PRL-secreting macroadenoma were all young males (case 4 and 17, Table 2).

Nevertheless, literature also reported the case of a 6.5-year-old girl with an invasive suprasellar pituitary macroadenoma [10] (case 5, Table 3).

In agreement with Goudet et al. [3], no pituitary tumor occurred before the age of 10 in our series of patients, although it could not be excluded that the real age of onset of the macroprolactinoma in our proband, which was diagnosed at age 13, was earlier. MEN1 Guidelines suggest an earlier beginning of the screening, at the age of 5 years [2] (Table 1). Some case reports of MEN1 children who developed pituitary tumors much earlier than the age of 10 are described and all three young patients had functioning macroadenomas with features of aggressiveness and treatment-resistance, thus suggesting a possible association between early development during childhood and aggressive biological behavior of pituitary tumors (cases 1, 2, and 5, Table 3) [6, 7, 10]. Diagnostic delay seems to be quite common, ranging from almost 1.5 years to 4 years [3, 6–8, 11] (cases 1–3, 6–8, Table 3), and it can severely compromise patients, particularly when pituitary tumors have an aggressive biological behavior.

According to current evidence [3], our series appears to show that prolactinomas were the most frequent MEN1-associated pituitary tumors in childhood, similar to adulthood.

Despite the absence of young MEN1 patients with pituitary-related chronic hypercortisolism in our series and the small number of these cases reported by Goudet et al. [3], at least six cases of children with MEN1-associated Cushing's disease have been described in literature [9, 11] (cases 4,6–8,9,10, Table 3).

Two cases of regularly screened MEN1 girls with pituitary tumors among the other manifestations of the syndrome are reported in Table 3 (cases 12 and 13) [12].

Although MEN1 syndrome was known not to be associated with a higher incidence of pituitary carcinoma [2], and no cases occurred in our series nor in the study of Goudet et al. [3], the case of a MEN1 boy who developed a TSH-secreting pituitary carcinoma at age 19 was reported in literature [13] (case 11, Table 3).

The crucial role of patient monitoring emerges from our series, as most patients with prolactinoma were clinically asymptomatic, because the screening allowed an early laboratory and/or radiological diagnosis prior to the development of clinical manifestations, granting early therapeutic intervention. Moreover, the occurrence of a pituitary adenoma during childhood and adolescence should lead clinicians suspect MEN1 disease. Indeed, a broad study analyzing 174 not-hypercalcemic patients with a sporadic pituitary macroadenoma showed that 3 out of 46 pediatric patients (≤18 years) suffered from MEN1, thus revealing that such adenomas were just "apparently" sporadic [14].

Considering the clinical triad of MEN1 [2], our limited series of children and adolescents showed that GEP-NETs were the rarest lesion in young MEN1 patients, in accordance with Goudet et al. [3]. To date, our patients developed only nonfunctioning pNETs, and no cases of other types of GEP-NET occurred in our study group, particularly no cases of insulinoma or gastrinoma have manifested.

Conversely, Goudet et al. [3] showed that insulinomas were the most frequent GEP-NET (12%), followed by nonfunctioning pNET (9%), and gastrinomas (2%) [3]. Data of Gonçalves et al. [15] seemed to confirm our evidence on nonfunctioning pNETs, showing a higher penetrance of nonfunctioning pNETs (42%) than insulinomas (11%) in MEN1 patients from age 12 to 20. The higher frequency of nonfunctioning pNET reported by Gonçalves et al. [15] with respect to Goudet et al. could be partly due to the systematic use of endoscopic ultrasound (EUS) to monitor young MEN1 patients, as EUS is more sensitive than MRI or CT and can reveal pancreatic tumors <1 cm in size in asymptomatic patients.

Based on the available literature, MEN1-associated insulinoma appears to have two main features: the precocity of its onset and its significant diagnostic delay both in the pediatric population [3] and in adulthood [16]. Symptoms of neuroglycopenia could be attributed to less rare diseases, such as epilepsy, and this could partly explain the diagnostic delay. Therefore, it is very important to start screening MEN1 patients for insulinoma beginning at the age of 5 [2, 3], and to educate the parents of MEN1 children to recognize clinical manifestations of insulinoma [3].

Table 3 shows two cases of children with insulinoma as the first clinical manifestation of MEN 1 [17, 18] (cases 14 and 15).

Nonfunctioning pNETs can usually be revealed through radiological investigation, because they are not hormone-

Table 3 Clinical cases of pituitary disease and pancreatic NET in MEN1 children and adolescents

Case number	Gender	Index case	First clinical manifestation(s) of MEN1	Age at diagnosis of the first clinical manifestation(s) of MEN1 (years)	Age at first clinical suspicion (years)	Other MEN1-associated lesions	Genetic information	Treatments	Reference number
1	M	Yes	Acceleration of growth and IGF1 excess-related facial features in presence of an invasive GH/PRL-secreting pituitary macroadenoma inducing optic chiasm compression	5	3.5 = acceleration of growth (+13 cm/year), and weight gain	Nothing	Familial MEN1 (His139Asp; exon 2)	Bromocriptine (ineffective); L-thyroxin for secondary hypothyroidism. Subsequently, transsphenoidaladenomectomy (not curative). Pergolide, then substituted by cabergoline (partial control of the disease) +octreotide (normalization of IGF1 levels)	6
	–	–	–	–	4 = worsening headache	–	–	–	
2	M	Yes	Visual disturbance caused by a giant prolactinoma with suprasellar extension inducing optic chiasm compression, severe hyperprolactinemia, and partial hypopituitarism (TSH and GH)	11	7 = chronic headache	Subsequent primary hyperparathyroidism	Familial MEN1 (consanguinity) (intronic mutation 784–9 G > A determining the synthesis of a truncated inactive protein)	L-thyroxin; cabergoline with late treatment-resistance and dual recurrence of pituitary disease, both times treated with surgical debulking (+RT after the 2° one) complicated by panhypopituitarism. Planned parathyroidectomy	7
	–	–	–	–	9.5 = progressive visual impairment	–	–	–	–
3	M	Yes	Visual disturbance, headache, mild nausea, height gain (+5 cm), and feet enlargement due to PRL/partially GH-secreting pituitary macroadenoma with suprasellar extension inducing obstructive hydrocephalus, bitemporalhemianopsia, and secondary hypogonadism	19	15 = induced galactorrhea	Simultaneous diagnosis of primary hyperparathyroidism and a partially cystic pancreatic tumor associated with increased levels of plasma insulin	Familial MEN1 (monosomy of chromosome 11 in pituitary adenoma)	Cabergoline (treatment-resistance), therefore transsphenoidal pituitary surgery	8
	–	–	–	–	18.5 = begin of overt clinical symptomatology	–	–	–	–
4	M	Not reported	*Cushing's syndrome due to an invasive pituitary microadenoma positive for ACTH (simultaneous presence of a pituitary macroadenoma positive for PRL)	*10	Not reported	Angiofibromas	Familial MEN1	Pituitary surgery (clinically curative)	9
5	F	Not reported	*Visual disturbance and acceleration of growth due to an invasive GH-secreting pituitary macroadenoma with suprasellarand lateral extension inducing optic chiasm compression	*6.5	Not reported	Not reported	Familial history of pituitary adenomas (c.765–6 C→T-splicing site; intron 3)	Transsphenoidal surgery; octreotide; subsequent pituitary surgery three additional times, then cabergoline, then RT with final persistence of biochemically active disease and radiological evidence of the adenoma, although reduced in size	10
6	M, twin	Yes	Cushing's disease due to pituitary microadenoma	13	9 = deceleration of growth	Primary hyperparathyroìdism with urolithiasis	Familial MEN1 (Tyr351His; exon 8)	Transsphenoidaladeno-mectomy at the time of the diagnosis	11
7	F	Yes	Cushing's disease due to pituitary microadenoma	11.5	7.5–8.5 = deceleration of linear growth and weight gain	Asymptomatic primary hyperparathy-roidism; lipoma of the shoulder	Familial MEN1 (Tyr351His; exon 8)	Transsphenoidaladeno-mectomy at the time of the diagnosis. Surgical removal of the lipoma at the age of 16	11
8	F	Yes	Cushing's disease due to pituitary microadenoma	12.5	9 = progressive obesity and deceleration of growth	Primary hyperparathyroidism	Non-familial MEN1 (Leu444Pro; codon 44 exon 9)	Transsphenoidaladeno-mectomy at the time of the diagnosis	11
9	M	Not reported	*Cushing's syndrome in presence of 2 pituitary microadenomas both positive for PRL and negative for ACTH plus a left adrenal lesion<1 cm in size	*15	Not reported	Primary hyperparathyroidism	Familial MEN1	Pituitary surgery (clinically curative)	9
10	M	Not reported	*Cushing's syndrome with normal hypophysis also at the surgical exploration; adrenal imaging not determined	*14	Not reported	Primary hyperparathyroidism	Familial MEN1	Blind left hemihypophysectomy (clinically curative)	9

Table 3 continued

Case number	Gender	Index case	First clinical manifestation(s) of MEN1	Age at diagnosis of the first clinical manifestation(s) of MEN1 (years)	Age at first clinical suspicion (years)	Other MEN1-associated lesions	Genetic information	Treatments	Reference number
11	M	Not reported	*Visual disturbance due to TSH-secreting pituitary carcinoma	*19	Not reported	Primary hyperparathyroidism; pancreatic islet cell tumors associated with liver adenomegaly; (slowly-growing periprostatic mass)	Not reported	Transfrontalhypophysectomy + RT; pituitary hormone replacement therapy. At the age of 28, occurrence of TSH-secreting carcinoma metastasis at foramen magnum, vertebral bodies, and intradural spinal level, which were surgically treated (+PTU); octreotide chronically. Total parathyroidectomy	13
12	F	no (screened patient)	Nonfunctioning NET with uncertain malignant potential of the neck of the pancreas; oligomenorrhea due to hyperprolactinemia associated with pituitary adenoma; asymptomatic primary hyperparathyroidism	14	–	–	Familial MEN1 (frameshift)	Partial pancreatectomy after an initial period of surveillance; cabergoline	12
13	F	no (screened patient since the age of 7)	Nonfunctioning NET with uncertain malignant potential of the distal segment of the pancreatic body; nonfunctioning pituitary microadenoma	12	–	–	Familial MEN1 (Gln349Stop)	Distal pancreatectomywith splenectomy	12
14	M	Yes	Seizures, hypoglycemic symptoms, and weight gain (8 Kg during 4 months) due to insulinoma (two pancreatic lesions)	8	8	Primary hyperparathyroidism at the age of 16; hyperprolactinemia with negative MRI at the age of 25	Familial MEN1 (IVS4–9G > A; intron 4)	Partial pancreatectomy; subtotal parathyroidectomy	17
15	F	Yes	Sudden loss of balance, tremors, and 5 min-long tonic-clonic seizures due to an insulinoma of the head of the pancreas	9	8 = begin of the weight gain (+10 Kg between 8 and 9 years old)	Nothing after 1 year of follow-up	Familial MEN1 (Asn374Argfs*3; exon 8)	Enucleation of the pancreatic mass	18

Notes: *it is not known whether the reported clinical manifestations (and the corresponding age of their diagnosis) truly represent the first clinical manifestation of onset of MEN1 syndrome

M male, *F* female, *IGF-1* insulin-like growth factor-1, *GH* growth hormone, *PRL* prolactin, *TSH* thyroid-stimulating hormone, *ACTH* adrenocorticotrophic hormone, *NET* neuroendocrine tumor, *PTU* propylthiouracil, *RT* radiotherapy, *MRI* magnetic resonance imaging, *cm* centimeters, *Kg* kilograms

producing, or they secrete insufficient amounts of hormones, such as PP or glucagon, to induce clinical signs and symptoms [2]. Consequently, as patients are asymptomatic, imaging screening is fundamental for a timely diagnosis.

Literature highlights the high frequency of nonfunctioning pNETs in young patients with MEN1 [15], the uncertainty of their biological behavior, and the need for a careful radiological monitoring of young MEN1 patients [12]. Two clinical cases of young girls with asymptomatic nonfunctioning pNETs with uncertain malignant potential were described by Newey et al. [12] (cases 12 and 13, Table 3).

Based on results from our study, we also recommend careful and regular monitoring of young MEN1 patients for nonfunctioning pNETs through radiological imaging and test for specific pancreatic hormones, such as glucagon and PP.

Little data on MEN1-associated gastrinomas in childhood is available because they are rare in children, as opposed to in adults [3].

Given the aggressive natural history of MEN1-associated gastrinoma during childhood, and the precocious age of onset [3], despite its rarity in pediatric MEN1 patients [2, 3], Goudet et al. proposed an early initiation of annual serum gastrin screening at the age of 10 [3]. However, normal levels of gastrin do not allow us to exclude the diagnosis of gastrinoma [3], and, therefore, secretin provocative tests might be helpful. Moreover, the restoration of normocalcemia after the treatment of PHPT in MEN1 patients with gastrinoma could normalize the level of fasting serum gastrin and the response to the secretin provocative test despite the presence of the gastrinoma itself, whereas the influence of the correction of PHPT-related hypercalcemia on the growth of MEN1-associated gastrinoma is not known

[19]. The importance of educating the parents of MEN1 children in the recognition of Zollinger-Ellison syndrome through its symptomatology is crucial [3].

To date, adrenal lesions have not manifested in our patients and very few data are currently available on adrenal lesions in MEN1 children and adolescents.

Pituitary-associated Cushing's disease appears to be more frequent than Cushing's syndrome caused by adrenal lesions in pediatric MEN1 patients [3, 9, 11].

The possibility of androgen hypersecretion in young MEN1 patients with an adrenal lesion should be kept in mind, which could reveal the presence of an adrenal carcinoma, a rare tumor that can be highly aggressive [3].

Another MEN1-associated tumor which is very rare, but extremely aggressive, is thymic NET [2, 3]. No cases of such a rare tumor occurred in our series, but both young MEN1 patients with a thymic NET described in the literature died early from metastatic disease [3, 20].

MEN1 Guidelines suggest regular monitoring for this tumor even after prophylactic thymectomy [2].

In conclusion, MEN1 seems to have partially different manifestations in children and adolescents than in adults, and this may be partly justified by different diagnostic approaches between the two groups. Despite the paucity of data in literature, current evidence highlights the fundamental importance of screening for tumors in young patients with MEN1 beginning in early childhood, because clinical manifestations can occur very early, even before age 5, but we do not have sufficient experience regarding very early onset of MEN1 disease. We also strongly recommend regular monitoring of young patients at high risk of developing MEN1-associated lesions beginning in early childhood. Clinicians must be continuously attentive to the earliest signs and symptoms of MEN1-associated tumors in order to avoid diagnostic delays that could seriously jeopardize the health and survival of young patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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

Informed consent Informed consent was obtained from all individual participants included in the study.

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