Fifty Years After the First Description, MEN 2B Syndrome Diagnosis Is Still Late: Descriptions of Two Recent Cases

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Background: Multiple endocrine neoplasia type 2B (MEN 2B) is a very rare syndrome characterized by a very peculiar phenotype with mucosal neuromas, marfanoid habitus, and bumpy lips associated with medullary thyroid cancer (MTC) and pheochromocytoma (PHEO). Although the syndrome was first described 50 years ago, it is still diagnosed too late, when the MTC is metastatic and frequently when the PHEO has already developed.

Case Presentations: We report on two cases of MEN 2B that were diagnosed too late, preventing a cure. The cases involve two females who were 25 and 12 years old. Both were previously treated for congenital skeletal abnormalities; however, despite their bumpy lips and mucosal neuromas, MEN 2B syndrome was not recognized. When they arrived at our center for both the presence of thyroid nodules and elevated serum calcitonin values, the MTC was already metastatic, and the older patient had already developed a bilateral PHEO. After 3 years and 1 year of follow-up, the two patients are still alive but with persistent structural and biochemical disease.

Discussion: These two cases show that knowledge of this syndrome is still insufficient and that the lack of knowledge impairs the ability to obtain an early diagnosis and cure. Because most patients with MEN 2B have no familial history, the only way to ensure a timely diagnosis is to recognize the MEN 2B phenotype on a clinical basis. **(*J Clin Endocrinol Metab* 104: 2520–2526, 2019)**

Although a partial description was reported by Wagenmann (1) and Froboese (2) in 1922, two series of 17 and 3 patients showing the association of medullary thyroid cancer (MTC) with pheochromocytoma (PHEO), mucosal neuromas, and marfanoid habitus were reported 50 years ago, in 1968 (3, 4). A few years later, in 1975, the association of MTC, PHEO, and mucosal neuromas was officially named *multiple endocrine neoplasia type 2B (MEN 2B)* by Chong *et al.* (5). Since that time, several other series have been published with accurate descriptions of a phenotype that includes bumpy lips; ocular alterations such as corneal fibers, conjunctival neuromas, conjunctivitis sicca, and tearless crying (6); intestinal symptoms related mainly to megacolon; and musculoskeletal abnormalities such as scoliosis, hip epiphysiolysis, and foot abnormalities (7, 8).

MEN 2B syndrome is rare, and it is the rarest (5%) among all MEN 2 syndromes, which include MEN 2A

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Abbreviations: CEA, carcinoembryonic; Ct, calcitonin; MEN 2B, multiple endocrine neoplasia type 2B; MTC, medullary thyroid cancer; PHEO, pheochromocytoma.

(35%), with the association of MTC, PHEO, multiple parathyroid adenomatosis, and cutaneous lichen amyloidosis, and familial MTC (60%), in which only MTC is inherited (9).

MEN 2B pathogenesis is related to the activation of the *RET* oncogene, which, in 95% of cases, is due to a missense point mutation determining an M918T change (10, 11). In a very few cases, the *RET*-activating mutation A883F has also been reported (12); almost anecdotally, two mutations (V804M/E805K) have been found in patients with MEN 2B (13).

In the majority of cases, patients show "*de novo*" *RET* mutations (6) of paternal origin, suggesting that a *RET* allele may be more susceptible to mutation when inherited from a father as opposed to a mother (14). This phenomenon may be due to the process of germ cell formation, which requires more divisions for males than for females, thus facilitating the occurrence of new mutations. Moreover, it seems that male gonads are more often exposed to mutagens; as a consequence, males have a higher probability of developing new mutations. The prevalence of these *de novo RET* mutations has been associated with more advanced age of the father (15). For this reason, the majority of patients with MEN 2B have a negative familial history, and they represent the index case.

Although some peculiar phenotypic features, such as mucosal neuromas (4) and constipation (16), are present from a neonatal age, most likely because of a negative familial history for the disease, the diagnosis is commonly made too late, when the MTC is already advanced and lymph node/distant metastases, as well as the PHEO, have already developed (17).

Here, we report the cases of two females with MEN 2B who, despite births in February 1992 and October 2005, were diagnosed too late, even though several doctors evaluated them for different reasons related to the main syndrome. Per the policy of our hospital, all adult patients or the parents of patients younger than 18 years gave written informed consent to use their clinical and biochemical data for research purposes and/or scientific publications.

Case Reports

Here, we report two cases of MEN 2B recently diagnosed in our center in females aged 25 years (Fig. 1) and 12 years (Fig. 2). Both of them were previously treated for congenital skeletal abnormalities, which, according to the type of alteration, are present in 20% to 40% of patients with MEN 2B (7). In both cases, several orthopedic surgical procedures were performed; unfortunately, none of the doctors who cared for these patients suspected a genetic syndrome. Of note, both of these patients had mucosal neuromas of the tongue (Fig. 1A and Fig. 2A), which are typical of and very frequent in MEN 2B. Although these neuromas were present since neonatal age, as reported by the parents of both girls, their pediatrician did not recognize these lesions as either diagnostic of MEN 2B or suspicious for a genetic syndrome. Both girls arrived for endocrinology observation only after a neck lump was visible and palpable. A late diagnosis of MTC accompanied by metastatic lymph nodes was made in both cases by cytology and measurement of serum calcitonin (Ct) level, which was 16,752 pg/mL in the older patient and 2487 pg/mL in the younger girl. At this point, both patients and their parents decided to contact our center for treatment of the MTC; immediately after their consultation, the clinical diagnosis of MEN 2B was made and then confirmed by evidence of a germline *RET* M918T mutation. A total body CT scan with contrast medium and a urinary metanephrine measurement were conducted in each patient to further investigate a possible PHEO.

Although the younger girl was unaffected, the older patient had bilateral PHEOs of 38 × 36 mm and 66 × 58 mm (Fig. 1D). Moreover, this patient had lung and bilateral neck lymph node metastases. A large megacolon was also present on the CT scan (Fig. 1D), a finding that had indeed been symptomatic for several years but was absolutely overlooked. The patient underwent surgery first for the PHEOs and then for the MTC, with an apparent complete removal of the thyroid and lymph nodes of the central compartment and latero-cervical chains. Histology confirmed the presence of MTC and C-cell hyperplasia. Four months after surgery, her serum Ct and carcinoembryonic antigen (CEA) levels were 5334 pg/mL and 53.5 ng/mL, respectively.

The younger patient had neither PHEOs nor other metastatic lesions, except lymph nodes in the neck. She had bumpy lips (Fig. $2A_1$), conjunctival neuromas (Fig. $2A_2$), and a clear marfanoid habitus (Fig. 2E). She underwent total thyroidectomy and neck lymphadenectomy, and histology confirmed the presence of MTC with C-cell hyperplasia and major invasion of the vessels, suggesting a rather highly aggressive disease. Although the surgical treatment was apparently complete, 3 months later her postoperative serum Ct and CEA levels were 155 pg/mL and 6.1 ng/mL, respectively.

The high levels of postoperative serum Ct and CEA in both patients are suggestive of persistent disease, which was already known in the older patient (*i.e.,* structural disease due to the lung and lymph node lesions) and unknown in the younger patient (*i.e.,* biochemical disease), for whom it will likely show up in the next few years.

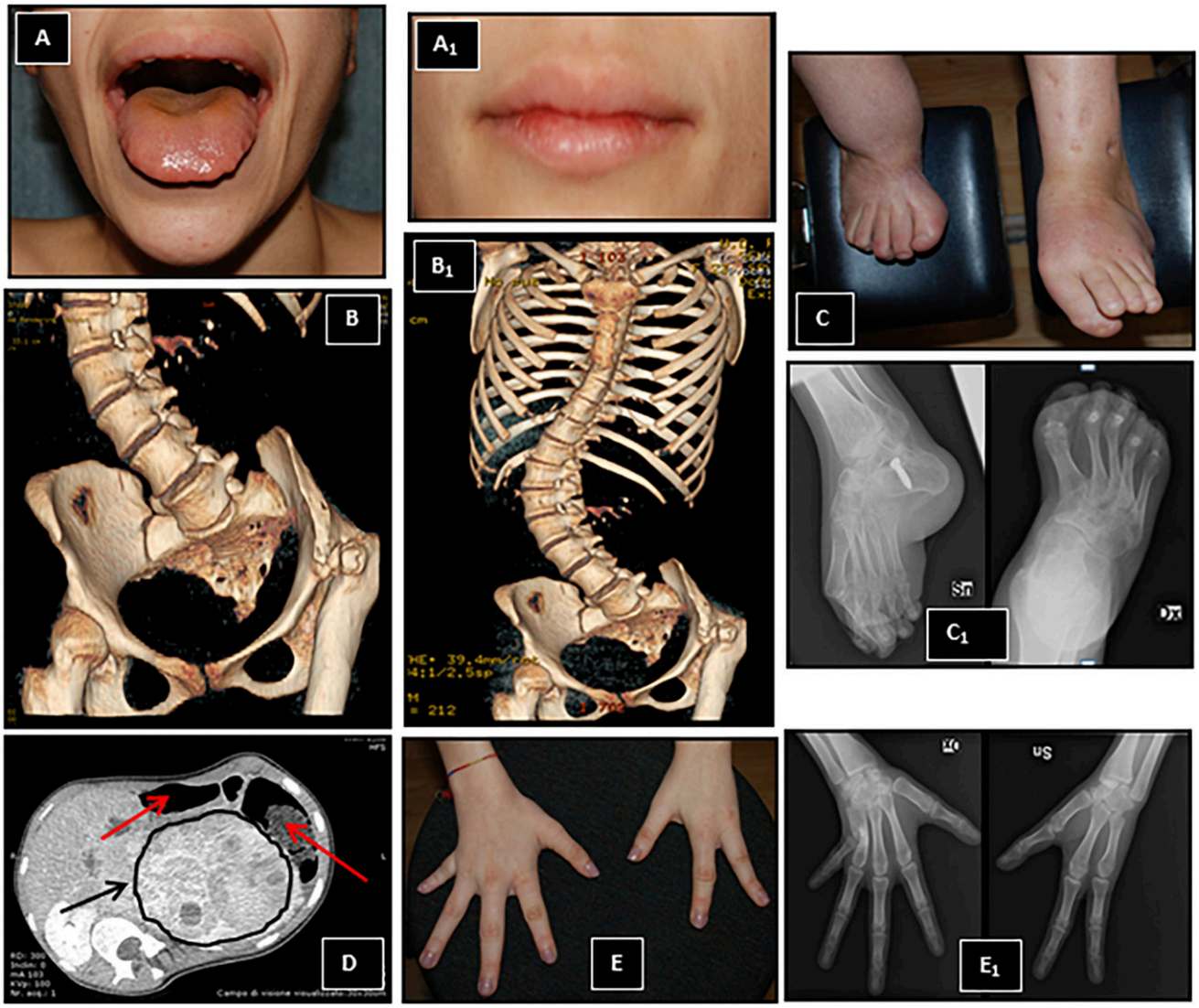

Figure 1. Typical physical features of the MEN 2B phenotype in the 25-year-old woman. (A) Mucosal neuromas of the tongue. (A_1) Bumpy lips. 3D CT scan reconstructions of the front view of the vertebral column and pelvis showing (B) scoliosis of t he column and (B_1) a severe hip epiphysiolysis of the left femur. (C) Congenital malformed feet already treated at the orthopedic level. (C_1) A screw implanted in the heel to improve the use of the left foot. (D) CT transversal abdominal section showing a large pheochromocytoma of the left adrenal gland (black arrow) and typical megacolon (red arrows). (E and E_1) Malformations of the hands with oligodactyly of the left hand and a shorter fifth finger of the right hand.

Other MEN 2B Cases in Our Center

Including the two previously described cases, in more than 30 years we have followed a total of 13 patients with MEN 2B, who represent 7.6% of all MEN 2 index cases (13 of 171) followed at our center. As in other series (6), all of these patients had a *de novo RET* M918T germline mutation, as neither parents nor other siblings carried the same DNA alteration. As shown in Table 1, their phenotypes were very similar, and all of them had bumpy lips (Figs. $1A_1$ and $2A_1$) and mucosal neuromas, primarily in the tongue (Figs. 1A and 2A) but also in the conjunctivas (Fig. $2A_2$), as occurred in the younger of the two females described here. All of them, including the 8-year-old girl in this series, had a marfanoid habitus with long arms and long legs with respect to the trunk; however, none of them had skeletal abnormalities similar to those of the two patients in this series (Figs. 1B–$1C_1$, 1E, and $1E_1$ and 2B and 2C). Thus, in our series, the prevalence of such skeletal abnormalities (2 of 13, 15.4%) is much lower than that reported in a German series of 21 MEN 2B cases (7).

The median age at diagnosis was 14 years, with a wide range from 8 to 37 years, which is very similar to the median age of the German patients with MEN 2B (7). In all cases but one, the diagnosis was made on the basis of a large mass in the neck region. One case, which occurred in the youngest among them, was diagnosed because of severe diarrhea at age 8 years; the doctor at the emergency department, where the parents brought the girl for

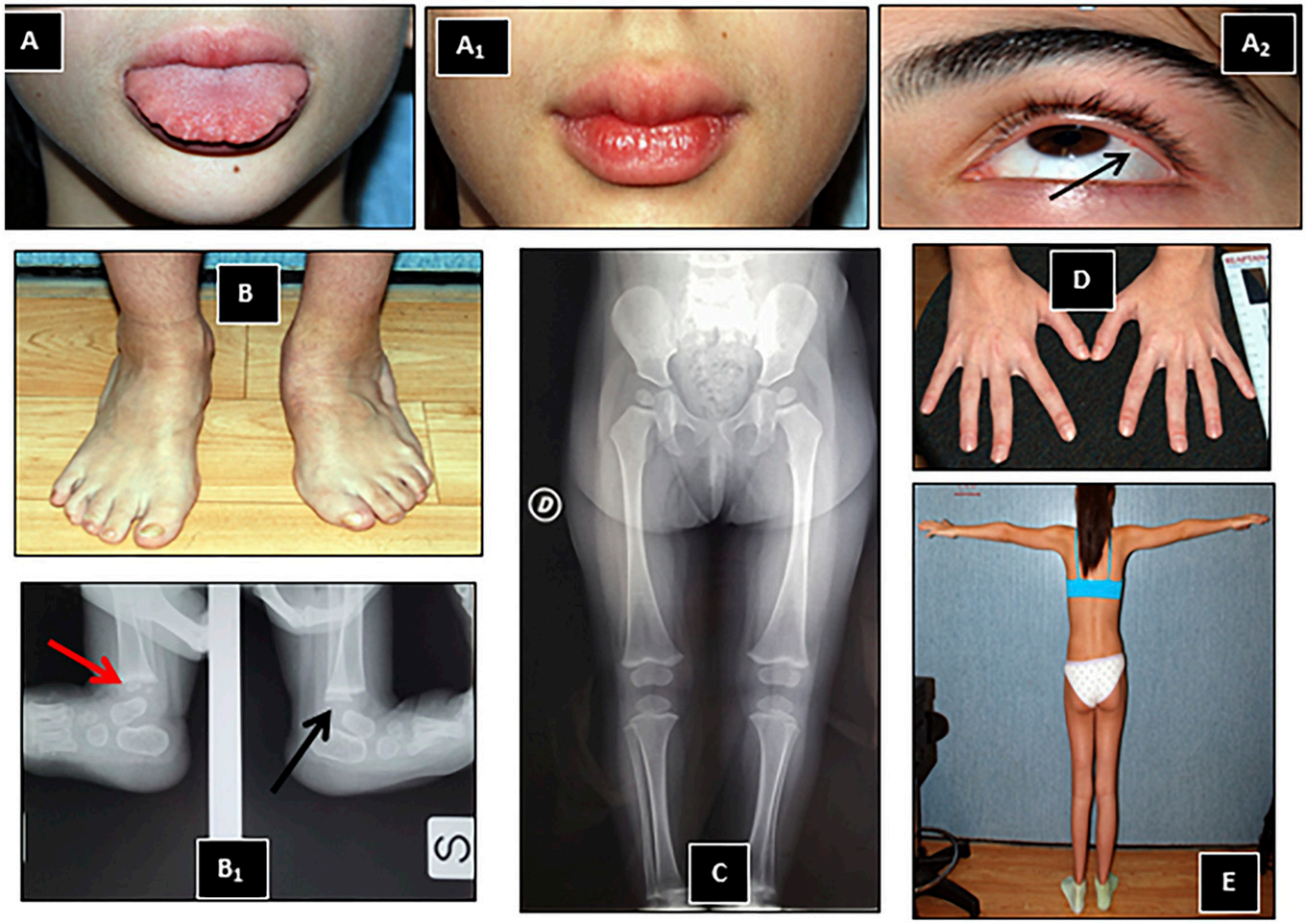

Figure 2. Typical physical features of the MEN 2B phenotype in the 12-year-old girl. (A) Mucosal neuromas of the tongue. (A_1) Bumpy lips. (A_2) Conjunctival neuroma indicated by the black arrow. (B) Congenital malformed feet, particularly evident in the left foot and (B_1) radiological findings showing the distal left tibial epiphysiolysis at 1 year of age. The red arrow shows the ossification nuclei that are absent in the left leg (black arrow). (C) Bilateral hip epiphysiolysis at 2 years of age. (D and E) Long fingers typical of the marfanoid habitus.

dehydration symptoms, identified a "strange" phenotype and asked for a genetic consultation. Nevertheless, the MTC had already advanced, and lung metastases were present.

Nine of 13 patients (69.2%) are still alive, with a median survival time from diagnosis of 9 years (range, 1 to 35 years). One of these patients (7.7%) is MTC disease free because the thyroidectomy was curative, with the tumor being completely intrathyroidal (T2N0M0). Of note, this girl received a diagnosis at age 14 years, similar to the other two girls who died as a result of the disease. Despite their similar age at diagnosis and type of *RET* mutation, their MTC stage at diagnosis was completely different, being very advanced in the two patients who died as a result of the disease versus being still intrathyroidal in the girl whose disease was cured.

The hypothesis that genetic background and/or the addition of other pathogenic event(s) may reinforce the already very high–transforming activity of the *RET* M918T mutation in some cases but not in others is plausible (18). Four of 13 patients (30.8%) died as a result of advanced MTC, two girls who were 13 and 14 years at diagnosis and who arrived at our center before the approval of vandetanib and two men aged 37 and 26 years whose MTC was very advanced (T4N1M1) and, in both cases, was complicated by an ectopic ACTH syndrome (19). The same mortality rate was reported in the series of German patients with MEN 2B (7).

After a median follow-up of 9 years (range, 1 to 35 years), 8 of 13 patients (61.5%) are still being followed up and have shown stable or slowly progressive disease without any therapy or, in two cases, with vandetanib treatment.

Discussion

MEN 2B is a very rare disease, with an incidence and prevalence that are unknown and can only be estimated. Taking into account the prevalence of new cases of MTCs in thyroid nodules (*i.e.*, ~0.2% to 0.5%) and the prevalence of MEN 2B in newly detected MTCs, the estimated prevalence of MEN 2B in the population

Table 1. Epidemiological, Clinical, and Pathological Data of Patients With MEN 2B Followed Up at the Pisa Center From 1983 to 2018

Case (Sex)	Year of Birth/Surgery	Surgical Treatment	TNM (7th Edition)	Ct Level Before Surgery (pg/mL)	Age at Last Follow-Up (y)	Systemic Therapy	Sites of Metastases at Last Follow-Up	MEN 2B Phenotype Expression	Outcome
Index case 1 (female)	1992/2016	TTx + CCLND and bilateral LCCLND	T3(m) N1b Mx	16,752	26	No	Lymph nodes, lung	MN, MH, MC, bilateral PHEO, SA, BL	Progressive disease
Index case 2 (female)	2005/2018	TTx + CCLND and right LCCLND	T2(m) N1b Mx	2487	13	No	No	MN, MH, SA, BL	Biochemical disease
Case 3 (female)	1985/1999	TTx + left LCCLND	T2 N0 Mx	>1300	15	No	No	MN, BL	Cured
Case 4 (female)	1992/2011	TTx + CCLND and right LCCLND	T2(m) N1b Mx	1140	26	No	Lymph nodes, lung	MN, MC, BL	Stable metastatic disease
Case 5 (male)	1998/2012	TTx + CCLND and left LCCLND	T3 N1b Mx	975	15	No	No	MN, MH, BL	Stable biochemical disease
Case 6 (female)	1999/2007	TTx + CCLND and bilateral LCCLND	T4a(m)N1b Mx	13,952	18	Yes (vandetanib)	Lung	MN, MH, BL	Stable metastatic disease
Case 7 (male)	1971/2008	TTx	T4(m) Nx Mx	1740	37	Yes (chemotherapy)	Bone, liver	MN, MH, MC, Bilateral PHEO, BL	Cancer-related death (2008)
Case 8 (male)	2005/No	/		1067	26	Yes (sorafenib)	Lymph nodes, bone, lung	MN, MH, left PHEO, BL	Cancer-related death (2009)
Case 9 (male)	1991/2004	TTx + CCLND and bilateral LCCLND	T3(m) N1b Mx	1500	27	Yes (vandetanib)	Lymph nodes, bone, lung, liver, pancreas	MN, MH, BL	Stable metastatic disease
Case 10 (male)	1958/1983	TTx	Tx Nx Mx	1673	60	No	Lymph nodes	MN, MH, MC, bilateral PHEO, BL	Stable metastatic disease
Case 11 (female)	1982/1995	TTx + CCLND	T3(m) N1a Mx	>20,000	20	Yes (imatinib)	Lymph nodes, lung, liver	MN, BL	Cancer-related death (2002)
Case 12 (female)	1972/1984	TTx + bilateral LCCLND	Tx N1b Mx	n.d.	19	No	Lymph nodes, liver, lung	MN, MH, MC, right PHEO, BL	Cancer-related death (1991)
Case 13 (male)	1998/2008	TTx + CCLND	T1a(m) N0 Mx	187.6	20	No	Lymph nodes	MN, MH, MC, BL	Stable metastatic disease

Abbreviations: BL, bumpy lips; CCLND, central compartment lymph nodes dissection; LCCLND, latero-cervical compartment lymph nodes dissection; MC, megacolon; MH, marfanoid habitus; MN, mucosal neuroma; n.d., no data; SA, skeletal abnormality; TTx, total thyroidectomy.

affected with thyroid nodules is ~0.005 to 0.007 per 100 persons. Thus, it is conceivable that general practitioners and doctors other than endocrinologists can miss the diagnosis. However, the phenotype of patients with MEN 2B is so peculiar that suspicion that the patient could be affected by a genetic syndrome should be high, as it was for the colleague who visited the 8-year-old girl in the emergency department.

Early diagnosis of MEN 2B is fundamental in curing the disease. Rohmer *et al.* (20) clearly demonstrated that when an early thyroidectomy is performed in children affected with MEN 2B (*i.e.*, when serum Ct level is still <30 pg/mL), the disease can be cured. However, the problem with the early diagnosis of MEN 2B is that most cases (all cases in our series) are *de novo*—without any family history to aid in the diagnosis. At variance, this is what happens for children affected by MEN 2A and submitted to *RET* genetic screening because of the discovery of the germline mutation in one member of the family (21).

Of note, despite the severity of the disease, which is related mainly to M918T, the *RET* mutation with the most aggressive transforming activity (22), patients with MEN 2B are surviving longer than expected, even when structural or biochemical disease is present and requires follow-up. This change in biological behavior is most likely due to improvements in diagnosis and surgical treatments (23). The recent use of tyrosine kinase inhibitors, such as vandetanib and cabozantinib (24, 25), has greatly improved survival rates as well.

In conclusion, knowledge of this syndrome is still insufficient. This is a major concern because the knowledge gap impairs a physician's ability to make an early diagnosis and subsequently cure the disease, particularly with MTCs. Because most patients with MEN 2B have no familial history, the only chance to achieve an early diagnosis and cure is through recognition of the MEN 2B clinical phenotype. Otherwise, suspicion of a genetic syndrome should alert general practitioners and/or pediatricians to send the child to a geneticist to verify a possible link between phenotype and genetic alterations. Once the diagnosis of MEN 2B syndrome has been made, these children must be referred to centers with a dedicated multidisciplinary team who can adequately care for them.

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