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RESEARCH ARTICLE

Multiple endocrine neoplasia type 2B: Frequency of physical stigmata—Results of the GPOH-MET registry

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Abstract

Background: Multiple endocrine neoplasia (MEN) 2B is characterized by early development of aggressive medullary thyroid carcinoma (MTC), visible physical stigmata, and associated symptoms. In most cases, de novo mutations are revealed. There are premonitory symptoms and stigmata that enable early diagnosis, before an inoperable MTC develops. The German Society for Paediatric Oncology and Haematology (GPOH)—Malignant Endocrine Tumours (MET) registry maintains records of children with MTC in Germany since 1997.

Methods: Children with a diagnosis of MTC in MEN 2B recorded in the GPOH-MET study were analyzed retrospectively. Stigmata and symptoms associated with MEN 2B were examined.

Results: From inception through 2017, 24 patients aged 0.2-17.3 years were included. Symptoms affecting the oral/dental (88.0%), musculoskeletal (79.2%), and gastrointestinal (70.8%) systems were recognized most frequently. Gastrointestinal and musculoskeletal symptoms preceded symptoms of MTC. Twelve patients had short stature. Regarding the prevalence of single symptoms, neuromas of the lips and the oral cavity were mentioned most frequently. Five patients died from MTC. Patients diagnosed by tumor symptoms showed more advanced disease than those with disease detected by other means. Children diagnosed via associated stigmata and symptoms or positive family history had significantly improved overall survival (OS) compared to children diagnosed via symptoms of MTC (OS 100% vs 53.3%).

Conclusions: In children with MEN 2B, oral/dental, musculoskeletal, and gastrointestinal symptoms are most common. If children are diagnosed via associated symptoms and stigmata, OS is improved. Most of the children were diagnosed with growth disturbances; this finding requires verification and ranging in other patient cohorts.

KEYWORDS
growth disturbances, medullary thyroid carcinoma, multiple endocrine neoplasia type 2B, stigmata

1 | INTRODUCTION

Multiple endocrine neoplasia (MEN) 2 is an autosomal dominant oncologic neurocristopathy characterized by multifocal medullary thyroid carcinoma (MTC), invariably with a background of C-cell hyperplasia.[1] Three distinct subtypes have been characterized with different incidence, genetics, age-related penetrance, aggressiveness of MTC, and association with other diseases. In MEN 2A besides MTC, pheochromocytoma, primary hyperparathyroidism, Hirschsprung disease, cutaneous lichen, and amyloidosis can occur. In other cases, MTC is isolated

Abbreviations: ATA, American Thyroid Association; GPOH, German Society for Paediatric Oncology and Haematology; MEN, multiple endocrine neoplasia; MET, malignant endocrine tumors; MTC, medullary thyroid carcinoma; OS, overall survival..

(familial MTC). In addition to calcitonin-producing thyroid tumors, pheochromocytoma, typical stigmata, and associated symptoms sometimes characterize children with MEN 2B.[2] MTC is usually the first tumor to occur and is the most common cause of death among these patients.[3] This malignancy is particularly aggressive in MEN 2B and may even occur in infancy.[4] Therefore, the current American Thyroid Association (ATA) guidelines recommend thyroidectomy in the first year of life, perhaps even in the first months.[5]

The pathogenesis of MEN 2B involves the proto-oncogene rearranged during transfection (RET).[6] This gene encodes a transmembrane receptor tyrosine kinase that activates multiple downstream pathways, promoting cell growth, proliferation, and survival. The vast majority of patients with MEN 2B harbour de novo mutations and have no sign of predisposition in their family history. It is crucial to recognize typical stigmata before the patient develops advanced MTC with a poor prognosis. Detailed description of the phenotype and age-related appearance may help to recognize patients before the development of advanced MTC with a poor prognosis.[7] A recent international, multicenter, retrospective study highlights the importance of early diagnosis with impact on overall survival (OS).[8]

2 | METHODS

The GPOH-MET 97 study, conducted by the German Society for Paediatric Oncology and Haematology (GPOH), created a prospective multicenter interdisciplinary national trial, which catalogues children and adolescents with malignant endocrine tumors (METs), including MTC. Since January 2013, the GPOH-MET 97 study has continued as the GPOH-MET registry. The GPOH-MET 97 study protocol and the GPOH-MET registry protocol were approved by the ethical committees of the University of Luebeck (97-125/23.12.1997) and Otto-von-Guericke-University Magdeburg (174/12, 20.12.12), Germany. Written informed consent was obtained from either the parents of the patients or the patients themselves, if 15 years of age or older, and was necessary for registration and follow-up.

Records were retrospectively reviewed for children with a histological diagnosis of MTC in MEN 2B who had been admitted from January 1996 through May 2017. All patients with only somatic RET mutations were excluded. All clinical features mentioned in the medical charts were collected and summarized for each child. Morphologic features and associated symptoms were analyzed as described by Kahn et al.[9]

Growth disturbances were included in this analysis because the musculoskeletal system is involved in MEN 2B. Disturbances of growth were defined as individual height below the third or above the 97th percentile for the corresponding mean height for a given age, sex, and population. If no precise body measurements were available, the diagnosis was made if it was mentioned by a physician or if hormonal therapy was provided.[10] The data of the German Health Interview and Examination Survey for Children and Adolescents (KiGGs 2003-2006) were used as reference population (Bundesblatt). Percentile curves and ranks were calculated using CrescNet.[11] Information regarding the heights of the parents was available in only a few cases. Weight for height percentage was used in children with short stature for nutritional assessment. The weight was compared with the weight (50th percentile) of a child of the same sex and height.

The time course of the disease and the development and recognition of the symptoms were not analyzed because the reporting was not sufficiently detailed in most cases. Pearson's chi-squared test was used to compare the frequency of categorical data. Student's *t*-test was used to compare the means of the two groups. OS was estimated using Kaplan-Meier survival analysis and compared using the log-rank test. Data analysis was performed using SPSS 24.0. Any finding with a *P*-value less than .05 was considered significant.

3 | RESULTS

3.1 | Patient characteristics

In total, 24 children (12 males, 12 females) with MTC in MEN 2B, aged 0.2-17.3 years (mean 9.6 years) at the time of thyroid surgery, were included. The registered patients were from unrelated kindreds. In 21 cases, MEN 2B was attributable to a mutation in codon 918 of RET. In three patients, no information on RET mutations was available, and diagnoses were made by family history and typical stigmata of MEN 2B. Most of the children (87.5%) harboured de novo mutations and had no sign of predisposition in their family history. In three cases, MEN 2B was diagnosed in first-degree relatives, and in three children, no information was available. The mean follow-up period was 5.9 years (0.2-18.6 years).

3.2 | Frequency of stigmata and symptoms associated with MEN 2B

The most frequent phenotypic characteristics affected the oral/dental (88.0%), musculoskeletal (79.2%), and gastrointestinal systems (70.8%) (Table 1). Regarding the prevalence of single symptoms, neuromas of the lips (often described as "bumpy lips"), the tongue, and the buccal mucosa were mentioned most frequently. Chronic constipation, often since infancy, was the second most frequent finding. If histological investigations were performed, intestinal ganglioneuromatosis was diagnosed in these cases. Furthermore, marfanoid habitus was described with the same frequency.

In addition to marfanoid appearance, growth abnormalities, deformities of the foot and hip, muscle hypotonia, and malpositions of the spinal column were recognized. Ocular manifestations were reported in more than half of the children. Chronic or recurrent conjunctivitis, mucosal thickening, and neuromas were registered most frequently. An inability to cry with tears was recognized by the treating physicians in four patients. Neuromas of the larynx were rarely detected.

3.3 | Growth disturbances in MEN 2B

Growth disturbances were detected in 14 of 24 (58.3%) patients. Eleven children showed heights below the third percentile and were

TABLE 1 Reported abnormalities associated with multiple endocrine neoplasia 2B, after Kahn et al[9]

System	Symptoms	Patients, n (%)	Mean age (range)
Oral/dental	All oral/dental symptoms	22 (88.0)	10.1 (0-17.5)
	Oral neuromas of tongue, lips, buccal mucosa	22 (88.0)	10.7 (0-18.9)
	Enlarged, nodular lips	21 (87.5)	11.4 (1.4-18.7)
	High-arched palate	5 (20.8)	12.8 (10.7-15.0)
	Gingival hyperplasia	3 (12.5)	11.9 (9.4-15.6)
	Prognathic mandible	3 (12.5)	12.2 (10.7-14.3)
	Spacing of anterior teeth	1 (4.2)	13.1
Musculoskeletal	All musculoskeletal symptoms	19 (79.2)	8.5 (0-16.4)
	Marfanoid habitus	16 (66.7)	13.6 (8.7-18.5)
	Growth disturbances	14 (58.3)	7.4 (0.5-15.5)
	Short stature	12 (50.0)	6.2 (0.5-13.1)
	Somatomegaly	2 (8.3)	14.6 (13.6-15.5)
	Foot or hip deformity	9 (37.5)	7.9 (0-16.1)
	Muscle hypotonia	7 (29.2)	7.6 (0-16.4)
	Lordosis/kyphosis/scoliosis	7 (29.2)	14.3 (8.3-22.6)
	Long, thin extremities	6 (25.0)	15.2 (10.7-22.6)
	Increased joint laxity	5 (20.8)	10.5 (3.6-14.6)
	Epiphysiolysis capitis femoris	3 (12.5)	13.9 (12.2-15.1)
Gastrointestinal	All gastrointestinal symptoms	20 (83.3)	5.2 (0-14.8)
	Chronic constipation or intestinal ganglioneuromatosis	16 (66.7)	4.2 (0-14.8)
	Low weight for height	8 (33.3)	5.4 (0-14.8)
	Cholecystitis	3 (12.5)	11.1 (6.5-14.4)
Ophthalmologic	All ophthalmologic symptoms	13 (54.2)	11.8 (5.2-17.4)
	Chronic/recurrent conjunctivitis	7 (29.2)	13.8 (5.4-19.6)
	Thickened eyelid margins or mucosal neuromas	6 (25.0)	13.2 (9.3-18.5)
	Tearless crying (decreased lacrimation)	4 (16.7)	11.0 (5.2-16.5)
	Thickened corneal nerves	3 (12.5)	11.5 (9.6-14.3)
Facies	All facial symptoms	12 (50.0)	9.8 (0-15.9)
	Long lower face	2 (8.3)	12.9 (10.7-15.0)
	Low-set ears	1 (4.2)	0.0
Otolaryngologic	Nasal, laryngeal, or bronchial mucosal neuromas	2 (8.3)	15.8 (14.2-17.3)
Other	Pubertal delay	3 (12.5)	14.1 (13.4-14.5)
Medullary thyroid carcinoma		12 (50.0)	12.1 (4.9-17.3)

diagnosed with dwarfism. One male was diagnosed with short stature, but no body measurements were available. The heights of two children were above the 97th percentile. In 21 of the children, body measurements were available for at least one time point. Growth charts for patients with growth disturbances are shown in Figures 1 and 2. One female was treated with the growth hormone, and at the time for which a height measurement was available, she showed catch-up growth (patient 19). The mean percentile of body height was 29.1 (range 0.1-98.6), and the mean z-score was −1.2 (range −5.9-2.2). A substantial proportion of registered patients presented with growth disturbances in pediatric endocrinology. Before thyroidectomy in eight children with growth disturbances, thyroid-stimulating hormone (TSH) levels were measured within the reference ranges. In one child with short stature, TSH was slightly elevated (5.45 mU/L). Bone ages were appropriate for age in two patients. IFG-1 and IGFBP-3 levels were low in two of five children. In one of three cases, the level of the growth hormone was low. In three children with short stature, the weight for height percentages were assessed to be below 70%.

3.4 | Age-related appearance of symptoms and stigmatas in MEN 2B

When examining the first evidence of symptoms, gastrointestinal disorders and musculoskeletal symptoms preceded with a significant margin the first symptoms of MTC (Breslau test, $P = .001$ and $P = .027$) (Figure 3). Chronic constipation or diagnoses of intestinal

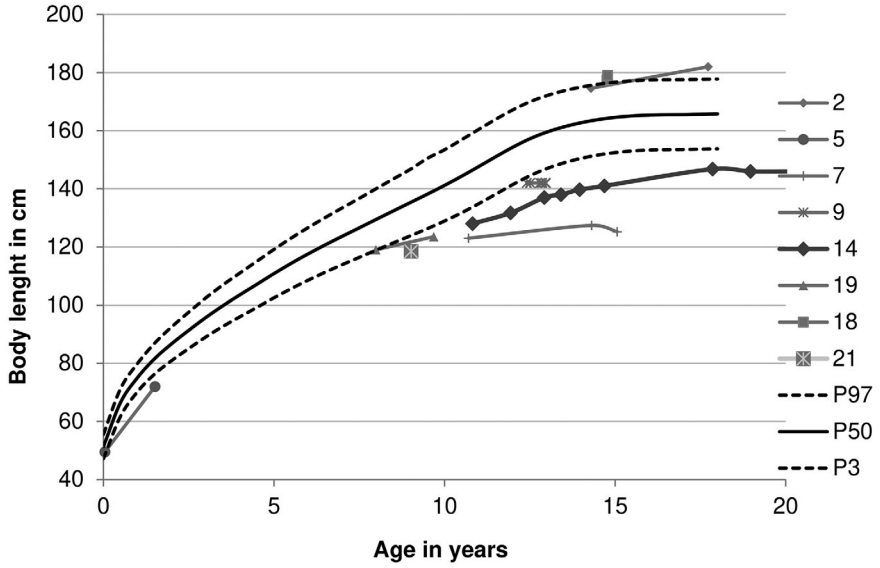

FIGURE 1 Growth charts of females with multiple endocrine neoplasia 2B and growth disturbances

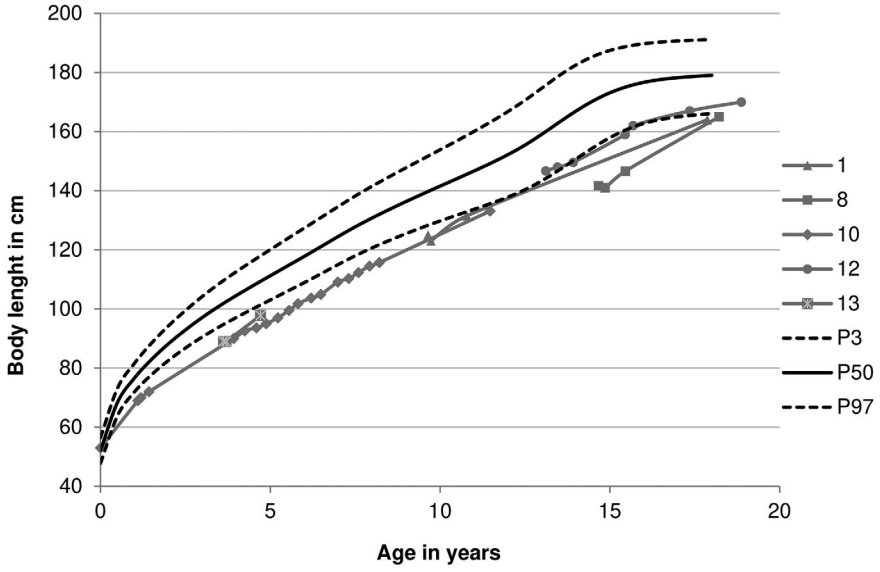

FIGURE 2 Growth charts of males with multiple endocrine neoplasia 2B and growth disturbances

ganglioneuromatosis were present in almost 30% of children at the age of one year. Oral and ophthalmologic signs of the cancer predisposition syndrome were not recognized frequently in early infancy. Nevertheless, a few infants were diagnosed with bumpy lips, foot deformities, or low weight for height.

3.5 | Outcome by type of diagnosis

Clinical presentations and extent of disease by type of diagnosis are shown in Table 2. In half of the cases, symptoms of MTC led to the diagnosis of MEN 2B at a mean age of 12.6 years. The signs and symptoms of MTC were an indolent cervival swelling in eight; stridor, dyspnoea, and coughing in two; and cachexia in one patient.

Typical stigmata associated with this cancer predisposition syndrome raised suspicion for MEN 2B in five cases. Four children suffered from chronic constipation that led to histological sampling and a diagnosis of intestinal ganglioneuromatosis. One child presented with short stature, and a tumor of the thyroid was diagnosed using the standard diagnostic approach. Children diagnosed from symptoms caused by MTC were significantly older at the time of thyroid surgery than children diagnosed from stigmata or associated symptoms (*t*-test, $P < .001$). Accordingly, the extent of malignancy was more advanced in children diagnosed via symptoms of MTC than in those diagnosed by other means—the tumors were larger, lymph node (pN1) and distant metastases (pM1) were more frequent, and extrathyroidal growth was more common. Biochemical cure, defined as an undetectable level of calcitonin, was achieved in only one of 12 patients recognized via tumor symptoms.

Five of the patients died from MTC. If MEN 2B was suspected because of physical signs or a positive family history, OS was significantly improved (OS 100% vs 53.3%, log rank, $P = .015$) (Figure 4).

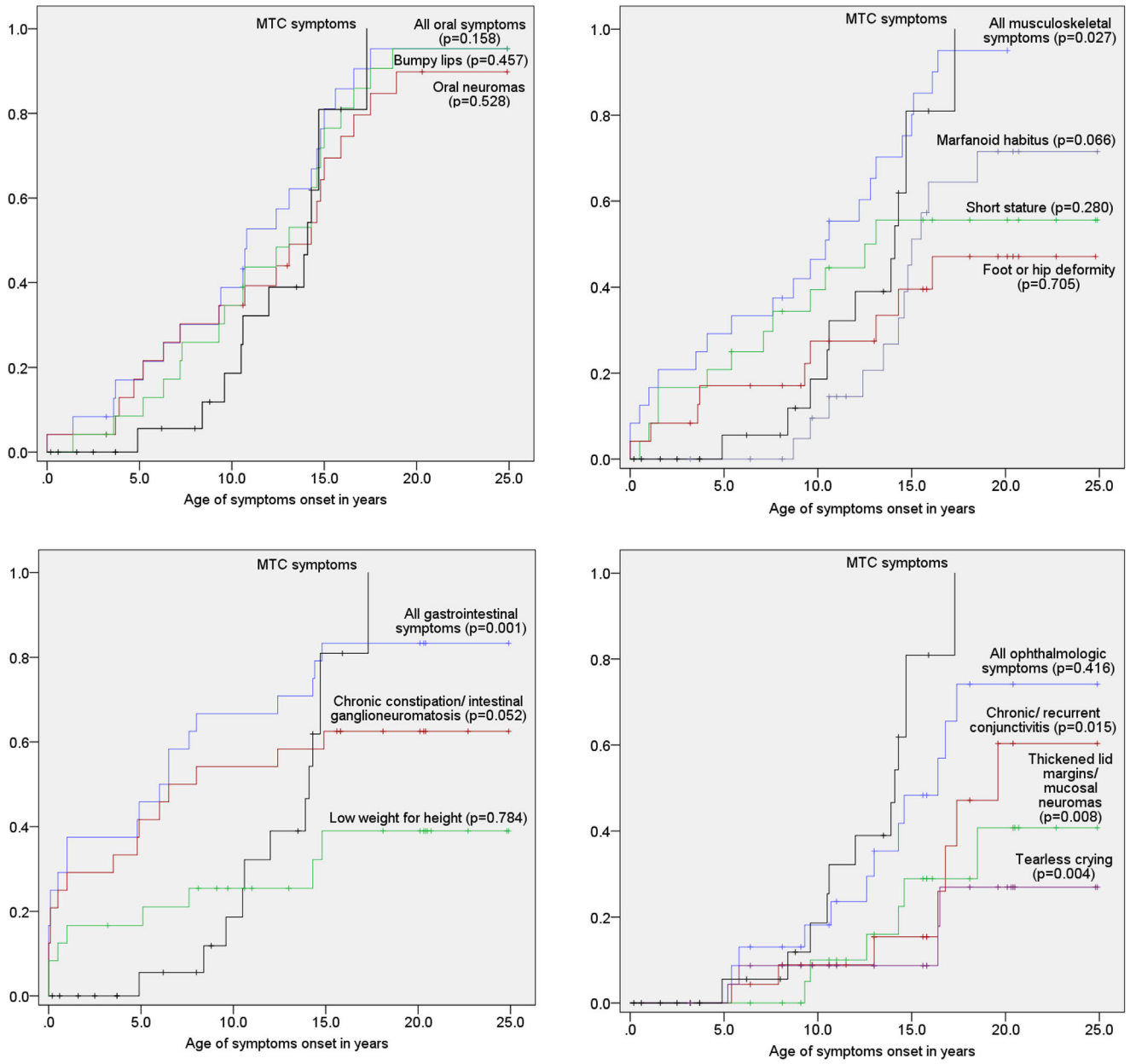

FIGURE 3 Appearance of stigmata and symptoms in multiple endocrine neoplasia 2B

4 | DISCUSSION

It is crucial to recognize children harbouring de novo RET proto-oncogene mutations that cause MEN 2B.[12] If affected children are identified before the development of advanced malignant disease, surgical cure is possible.[7] The aim of this retrospective analysis was to collect all the different characteristics in as much detail as possible. The impact on clinical course and outcome should also be determined.

In our data, oral and dental findings were the most frequent manifestations, followed by musculoskeletal and gastrointestinal signs. It is important to draw the attention of pediatricians and physicians to that finding, enabling them to diagnose patients early. According to the current ATA guidelines, MEN 2B and RET mutation in codon 918 carry the highest risk levels.[5] In affected patients, genetic testing and prophylactic surgery are recommended to be completed as soon as possible.

A literature review on the topic mostly revealed case reports and small case series. The most comprehensive analysis dealing with clinical features of MEN 2B and their appearance over the lifespan was published by Brauckhoff et al.[13] Those investigators sent the parents of affected children a questionnaire centering on pregnancy, delivery, symptoms during the first year of life, and the symptoms leading to the diagnosis of MEN 2B. Clinically healthy age- and sex-matched infants served as controls. The team found that crying without tears was the ideal premonitory symptom. This feature appeared at a mean age of 0.15 years and was present in 91% of cases. In our investigation, however, physicians mentioned this feature in only four cases. The different results may be due to the dissimilar approaches used. The parents may

TABLE 2 Considerations leading to diagnosis and extent of medullary thyroid carcinoma (MTC)

	Symptoms of MTC	Stigmata and symptoms	Family history of multiple endocrine neoplasia 2B	*p*-value
Patients	12	10	2	
Mean age in years (range) at MTC surgery	12.6 (5.2-17.3)[a]	7.6 (0.2-15.9)[a]	1.6 (0.6-2.5)	[a]$p < 0.001$
Preoperative CTN, mean	17 119 pg/mL[b]	4475 pg/mL[b]	148 pg/mL	[b]$p = 0.376$
Preoperative CTN, range	283-105 416 pg/mL	45-24 200 pg/mL	105-191 pg/mL	
Tumor size in cm (range)	2.6 (1.5-4.1)[c]	0.9 (0.2-2.5)[c]	0.3 (0.2-0.3)	[c]$p = 0.005$
Extrathyroidal, n (%)	8/10 (80)[d]	2/9 (22)[d]	0/2 (0)	[d]$p = 0.012$
pN1, n (%)	12/12 (100)[e]	4/10 (40)[e]	0/2 (0)	[e]$p = 0.001$
pM1, n (%)	8/12 (67)[f]	1/10 (10)[f]	0/2 (0)	[f]$p = 0.012$
Postoperative CTN, mean	26 412 pg/mL[g]	7815 pg/mL[g]	11	[g]$p = 0.468$
Postoperative CTN, range	(3-106 250)	(2-53 904)	(4-19)	
Biochemical cure, n (%)	1/12 (8)[h]	5/10 (50)[h]	1/2 (50)	[h]$p = 0.029$
Mean follow-up in years (range)	4.6 (0.5-10.8)	8.0 (0.2-18.6)	4.1 (2.6-5.6)	
Overall survival 10 years (%)	53.3[i]	100[i]	100%[i]	[i]$p = 0.015$

Abbreviation: CTN, calcitonin.

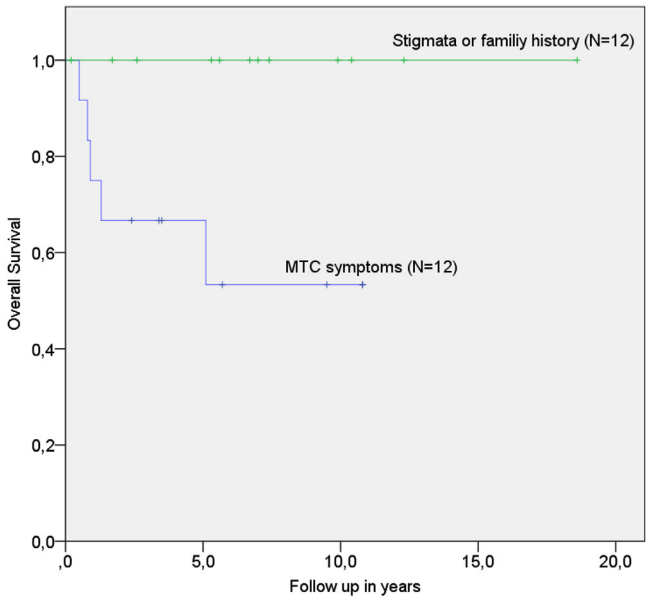

FIGURE 4 Considerations leading to diagnosis and overall survival

have considered tearless crying a harmless feature and failed to report it to the treating physicians.

In the data from the GPOH-MET registry, oral and dental stigmata were the most common manifestations. Overall, 23 of 24 patients had conspicuous oral, dental, and/or facial symptoms. Among these findings, neuromas of the tongue, lips, and buccal mucosa were described most frequently. Syndromic oral findings indicative of MEN 2B have been noted since the beginning of the last century. In 1976, Carney et al reported on 16 cases with oral abnormalities examined at the Mayo Clinic and reviewed 51 additional cases published to that date.[14] Those investigators summarized the mucosal involvement in MEN 2B and proposed a predilection for the centrofacial region, with the central portion of the lip and the tip of the tongue being most affected. The oral lesions, although asymptomatic and benign, can cause considerable psychological distress.[15] Affected patients may consult an oral and maxillofacial surgeon or an orthodontist because of labial nodules or malocclusion.[16,17] Even those types of practitioners should be aware of the significance of these findings. MacIntosh et al described the maxillofacial appearance of five patients.[18] In all the subjects, prominent lips, oral lesions, macroglossia, central diastema, and apertognathia were evident. Lesions of neural origin are rare in the oral and maxillofacial region, representing less than 1% of cases submitted to oral pathology laboratories.[19] In a retrospective study of 340 neural neoplasms of the oral cavity, only one patient was diagnosed with multifocal mucosal neuroma as a component of MEN 2B.[20] Almost all specific signs develop in an age-related manner. Mucosal neuromas leading to bumpy lips are not always present in early childhood.[21]

Gastrointestinal symptoms are common in MEN 2B, reaching an incidence of 70% to 97%.[8,22,23] Intestinal ganglioneuromatosis causing chronic constipation was present in 16 patients in the GPOH-MET registry but led to diagnosis in only four patients. Gastrointestinal discomfort was the most promising premonitory symptom before the development of MTC symptoms. A review has been conducted on 55 patients with a special focus on gastrointestinal symptoms prior to the diagnosis of MEN 2B.[24] The most common symptom by far (73.0%) was constipation, followed by diarrhea (29.1%), failure to thrive (11.0%), abdominal distension (14.5%), and vomiting (10.9%). In 29 of 55 patients, the first signs of gastrointestinal symptoms were present at birth or during the first year of life. Intestinal ganglioneuromatosis led to an investigation for MEN 2B in 15 patients. Camacho et al described four patients diagnosed with MEN 2B and advanced MTC due to late diagnosis.[25] In all four patients, chronic constipation had been present since infancy. It cannot be stressed enough that severe chronic constipation since early infancy

should be followed up and investigated.[26,27] Constipation is the second symptom appearing in the course of life, according to Brauckhoff et al.[13] Many patients report constipation during early childhood, later to be intermittently relieved by diarrhea.[15,21]

Marfanoid habitus is assumed to be present in the majority of patients with MEN 2B.[23] The label "marfanoid habitus" is a collective, nonspecific term that is difficult to standardize. This manifestation is characterized among other manifestations by large hands and feet, long extremities, and an elongated face. Many of the patients included in the present study were described as marfanoid without a complete list of single symptoms. In addition to MEN 2B, marfanoid habitus is reported in Perrault syndrome, Lujan-Fryns syndrome, and Shprintzen-Goldberg syndrome, to name just a few.[28–30]

In this retrospective analysis of affected children in Germany, a significant proportion showed growth disturbances. More than half of the patients were diagnosed with short stature. All patients were from unrelated kindred, which excludes a bias arising from hereditary growth disturbances of other etiology. Growth failure due to hypothyroidism was not present in any of the children. In 40% of the cases, low levels of IGF-1 and IGFBP-3 were detected. That may hint at the diagnosis of a growth hormone deficiency. In addition, the nutritional status is an important determinant of the growth hormone-IGF axis. Children with malnutrition show high levels of the growth hormone and low levels of IGF-1 and IGFBP-3.[31] Further research is needed on possible causes. Growth charts were analyzed and illustrated to confirm this surprising finding. Regarding body height and MEN 2B, only a few case reports have been published.[32] A 15-year-old male reported on by Nelson et al in 1979 presented with short stature.[33] That patient's height was above the 50th percentile at the age of 6 years, but 8 years later, his height was in the third percentile. The authors assumed that many factors, including intestinal malabsorption and excess calcitonin, may have influenced the slowing of the patient's growth. Severe malnutrition was present in three children with short stature. One male had a normal weight for length percentage at the age of 9.6 years and a ratio below 70% from the age of 10.8 years. It is difficult to settle on what comes first. Does intestinal malnutrition impair growth in children with MEN 2B? Carney et al described 21 patients with MEN 2B in 1981.[34] Eleven of those patients were members of three families. Five patients showed growth disturbances—four were diagnosed with dwarfism and one showed height above the 97th percentile of the corresponding peer group. Because little has been published regarding body height in MEN 2B, further verification of our findings is necessary. To our knowledge, although growth disturbances have been described in patients with MEN 2B, a general association has not yet been drawn. The quality of the anthropometric measures is low in the current investigation, with the parents' heights missing.

There are a number of case reports dealing with ophthalmologic signs of the disease.[35,36] Critical findings could be possible if the patient is examined by an ophthalmologist or an oculoplastic surgeon.[37] Prominent corneal nerves, thickening of the eyelids, and subconjunctival neuromas are frequently reported. In a review of 33 published cases, prominent corneal nerves were a striking ocular characteristic of MEN 2B.[38] In the present analysis, not all children were examined by ophthalmologists. Therefore, the incidence of ocular findings may be underestimated. Some of the ocular features are asymptomatic and may go unnoticed by the patient and the physician.

Laryngeal neuromas appear to be very rare in MEN 2B. Only a few patients have been reported in the literature.[39,40] In our data, two of 24 (8.3%) children were diagnosed with neuroma localized in the larynx. Such growths can manifest as potentially airway-compromising lesions.[41]

The way children with MEN 2B were identified had an impact on the extent of tumor spread and outcome in our data. If children were detected via tumor symptoms, lymph node metastases were present in all cases, and distant metastases were detected in two thirds of cases. A study including 44 children and adults described similar results.[7] Biochemical cure, the most favorable result for a patient with MTC, was achieved in half of the children with MEN 2B in the GPOH-MET registry after recognition of associated stigmata and symptoms. If a patient has a calcitonin level below the lower limit of detection, he/she has, approximately, a 3% chance of recurrent disease during follow-up.[42] There is a close correlation between age at the time of thyroid surgery and outcome.[7,22] A child with inherited MEN 2B underwent prophylactic surgery at the age of 0.6 years. No metastases were detected, but at the last follow-up (2.6 years later), the patient's calcitonin level was 42.7 pg/mL. Long-term data demonstrate improved survival for patients treated in the new millennium compared to patients treated before the year 2000.[43] It is possible that greater awareness of the phenotype led to earlier diagnosis and fewer patients with advanced disease.

In our data, among stigmata and associated symptoms, intestinal ganglioneuromatosis leading to chronic constipation was the most promising symptom indicative of MEN 2B. When this symptom led to the early diagnosis of MEN 2B, the extent of the tumors was rather limited and biochemical cure was usually achieved. Similar results were outlined by Brauckhoff et al in 2014.[7]

This retrospective analysis of the GPOH-MET registry has a few limitations. The study is not a systematic query of the existence of all associated features. These analyses represent the clinical symptoms recognized by the physicians and gathered from medical reports. The frequencies of all symptoms are probably underestimated. Furthermore, the chronology of symptom appearance is not outlined.

In this analysis of the clinical features of children included in the nationwide multicenter GPOH-MET registry over 20 years, oral/dental symptoms were most frequently detected, followed by musculoskeletal and gastrointestinal symptoms. Whether the diagnosis was based on symptoms of MTC or stigmata had a significant impact on outcome. Furthermore, this report is the first to assess growth disturbances and their association with MEN 2B.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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