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Multiple Endocrine Neoplasia Type 2B Presents Early in Childhood but Often Is Undiagnosed for Years

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Abstract

We describe the presenting symptoms and signs of multiple endocrine neoplasia type 2B in a cohort of children. Improved awareness of the early nonendocrine signs of multiple endocrine neoplasia type 2B could lead to earlier diagnosis before the development of medullary thyroid cancer and possibly its metastasis.

Multiple endocrine neoplasia type 2B (MEN2B) is a rare, but often fatal, hereditary autosomal-dominant cancer syndrome, caused by activating germline mutations in the *RET* proto-oncogene (M918T in about 95% of patients with MEN2B).^{1–3} This syndrome is characterized by early onset medullary thyroid cancer (MTC), pheochromocytoma, and typical extraendocrine features, including marfanoid habitus and other skeletal abnormalities, mucosal neuromas, and ganglioneuromatosis of the gastrointestinal (GI) tract (Figure). Because 90% of patients carry de novo mutations, diagnosis of MEN2B may not be made until late childhood or adolescence, when MTC has already developed and even metastasized.^{4,5} Improved awareness of the early nonendocrine signs of MEN2B could lead to earlier diagnosis and intervention in these patients. The aim of this report was to describe the initial symptoms and/or signs that preceded diagnostic evaluation for MEN2B in a cohort of pediatric patients. The majority of these patients were previously evaluated for an MEN2B-related symptom (or combination of symptoms); however, these symptoms were not attributed to MEN2B at that time.

Methods and Results

We performed a retrospective chart review of all patients with MEN2B evaluated at the National Institutes of Health from July 2007 to February 2018. All patients were enrolled in a National Cancer Institute, Pediatric Oncology Branch, larger natural history study (NCT01660984) of MEN2 that was approved by the National Cancer Institute Institutional Review Board.

A total of 38 patients with MEN2B were identified (21 males and 17 females). The mean age at diagnosis was 10.6 ± 3.9 years (Table). M918T *RET* mutation was found in all patients. Of the 35 sporadic cases, 22 were diagnosed with MEN2B after they presented with an endocrine manifestation (group 1), including pheochromocytoma ($n = 1$), neck mass owing to MTC ($n = 17$), respiratory difficulties owing to intrathoracic tumor invasion ($n = 3$), or a combination of thyroid mass and skeletal abnormalities in 1 patient who was noted to have marfanoid habitus during preoperative evaluation for a slipped femoral capital epiphysis. The remaining 13 patients presented with a nonendocrine manifestation (group 2): oral neuromas ($n = 7$), corneal nerve abnormalities ($n = 3$), persistent diarrhea ($n = 1$), a combination of mucosal neuromas with failure to thrive ($n = 1$), or skeletal abnormalities with inturning feet causing frequent falls as a toddler ($n = 1$). The mean age at diagnosis was not statistically different between the 2 groups (Table).

Twenty-one patients from both groups had 1 or more physician referrals for the evaluation of an MEN2B-related feature at 5.0 ± 3.2 years before the diagnosis of MEN2B. Five patients (3 from group 1 and 2 from group 2) were previously referred for evaluation of tongue lesions and were diagnosed with geographic tongue, tongue papillomatosis, or behavioral/benign lesions at a mean period of 4.6 ± 2.6 years before their MEN2B diagnosis. Twelve patients (5 from group 1 and 7 from group 2) were previously evaluated for severe diarrhea and/or constipation or failure to thrive at a mean period of 5.2 ± 3.8 years before their MEN2B diagnosis. Seven patients (3 from group 1 and 4 from group 2) were previously seen owing to musculoskeletal (MSK) complaints, including persistent bone pain, hip/knee dislocations, leg length discrepancy with clubfoot, generalized myopathy with bilateral pes cavus, and repeated bone fractures after minor injuries at a mean period of 5.1 ± 2.9 years before their MEN2B diagnosis. Of these, 2 patients were evaluated for a combination of GI and MSK complaints.

The outcomes of a subset of patients on the management of MTC have already been published elsewhere.⁶

Discussion

Early diagnosis is critical for the optimal care of patients with MEN2B. Because MTC develops very early in life and remains the leading cause of death in MEN2B, current American Thyroid Association guidelines recommend prophylactic thyroidectomy before the age of 1 year in patients with a known M918T mutation. A potential implication of early diagnosis may be curative surgery. Brauckhoff et al showed that MTC was potentially

curable if thyroidectomy was performed up to the age of 4 years in a cohort of 41 patients with MEN2B with de novo mutations.⁷

Early recognition of MEN2B remains a challenge for physicians, because most of the typical MEN2B phenotypic stigmata develop gradually over time in an age-dependent fashion, with essentially all patients exhibiting 1 or more of these symptoms by the time that MTC is diagnosed. Brauckhoff et al investigated the early clinical manifestations of 25 patients with MEN2B and reported that fewer than 20% of patients had the typical MEN2B features during their first year of life.⁸ However, at a median age of 16.2 years, all patients had developed MTC along with oral (96%), ocular (91%), GI (71%), and MSK (75%) manifestations, as well as pheochromocytoma (28%).

An index of suspicion for MEN2B should be maintained when evaluating patients with a combination of relatively common pediatric issues. These presentations can include failure to thrive with feeding difficulties in infancy, persistent constipation and/or diarrhea requiring extensive GI evaluation, and unexplained MSK symptoms. MSK findings include foot anomalies, such as pes cavus or talipes equinovarus; spine abnormalities, such as scoliosis, kyphosis, and lordosis; or persistent bone pain and/or fractures after minor injuries, sometimes with slipped femoral capital epiphysis. In patients among whom MEN2B is suspected, further evaluation should include serum calcitonin level and genetic testing for *RET* mutations.

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Glossary

GI	Gastrointestinal
MEN2B	Multiple endocrine neoplasia type 2B
MSK	Musculoskeletal
MTC	Medullary thyroid cancer

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Figure.
A, Marfanoid habitus and GI ganglioneuromatosis. **B,** Oral mucosa neuromas.

Table.

Patients with MEN2B with de novo mutations

Patients with MEN2B with de novo mutations	Number of patients	Age at diagnosis, years
Presenting with endocrine manifestations (group 1)	22	11.8 ± 3.6
Presenting with nonendocrine manifestations (group 2)	13	9.9 ± 3.5
Groups 1 and 2 combined	35	10.6 ± 3.9