Extra-endocrine phenotypes at infancy in multiple endocrine neoplasia type 2B: A case series of six Japanese patients

Rie Matsushita1, Akihiro Sakurai2, Kanshi Minamitani3, Masanori Yamazaki4, and Shinya Uchino5

1Division of Pediatrics, Kikugawa General Hospital, Shizuoka, Japan
2Department of Medical Genetics and Genomics, Sapporo Medical University School of Medicine, Sapporo, Japan
3Department of Pediatrics, Teikyo University Chiba Medical Center, Chiba, Japan
4Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan
5Department of Surgery, Noguchi Thyroid Clinic and Hospital Foundation, Oita, Japan

Abstract. Multiple endocrine neoplasia type 2B (MEN2B) is an extremely rare disease, most often caused by a de novo p.Met918Thr RET mutation. Medullary thyroid carcinoma of MEN2B has a good prognosis if diagnosed by one year of age. However, diagnosis of MEN2B within the first year of life is markedly challenging owing to its high de novo occurrence and lack of clarity in terms of extra-endocrine symptoms that could aid early diagnosis. Herein, we present six cases of Japanese children with MEN2B harboring the p.Met918Thr RET variant. Exploratory data extraction was conducted using a questionnaire. The patients underwent thyroidectomy at a median age of 11 yr (range, 6–19 yr). Four of the six patients underwent neonatal hospitalization at birth without complications, and three tested positive for neuroblastoma screening at infancy. The patients presented at least one MEN2B-associated symptom before one year of age, including ganglioneuromas, pseudo-Hirschsprung disease, alacrima, bumpy lips, sucking disability, or decreased muscle tone, along with other suspected comorbidities, such as Williams or Prader–Willi syndrome. This case series demonstrates that MEN2B manifests through several extra-endocrine symptoms by the age of one year.

Key words: extra-endocrine phenotype, multiple endocrine neoplasia type 2B, ganglioneuroma, bumpy lip, neuroblastoma screening

Introduction

Multiple endocrine neoplasia type 2B (MEN2B) is a rare syndrome affecting 0.9–1.6 in one million individuals (1). The incidence of MEN2B in Japan remains unclear. Endocrine symptoms include pheochromocytoma and medullary thyroid carcinoma (MTC), which are the primary causes of mortality. MTC often occurs during early infancy; patients who undergo thyroidectomy at one year or younger have a better prognosis, with an 83% cure rate and no MTC-related deaths reported (2). Therefore, the American Thyroid Association guidelines recommend total thyroidectomy before this age and, if possible, by one month (3). However, in Japan, guidelines on the recommended age for such surgeries are lacking.

In most cases, MEN2B is caused by a de novo p.Met918Thr gain-of-function mutation in the RET proto-oncogene, which, coupled with the difficulty in recognizing early symptoms due to the rarity of the disease, renders early diagnosis before the clinical onset of MTC extremely difficult (2, 4).

Numerous patients with MEN2B present one or more extra-endocrine features manifesting as bumpy lips, mucosal neuroma, constipation, foot abnormalities, and alacrima (5), which are hallmarks for an early diagnosis. Nevertheless, numerous extra-endocrine symptoms, which are difficult to detect by one year of age among patients with de novo mutations, are believed to appear gradually (2, 5). Furthermore, owing to the rarity of the disease, few studies have reported early extra-endocrine symptoms. The purpose of this descriptive study was to discover clinical symptoms that may contribute to the early diagnosis of MEN2B by comprehensively accumulating clinical symptoms of MEN2B from birth in a case series.
Patients and Methods

In this case series, we report all six MEN2B cases from the “Alliance of patients with MEN and family members” (Mukuroji-no-kai) project conducted in Japan, presenting one or more endocrine symptoms and were diagnosed by genetic testing. The cooperation of all six individuals was sought. We excluded patients who had not been genetically diagnosed, did not present one or more endocrine symptoms, or refused to participate; however, none were excluded. The questionnaire survey requested information such as age, sex, age at the time of diagnosis, suspected disease, the reason for and timing of diagnosis of the suspected disease, presence of a genetic mutation, family history of MEN2B, birth height/weight/head circumference/method of delivery, condition at birth, parents’ age, description of previously unreported symptoms, age at the appearance of symptoms, and height/weight/head circumference over time until adolescence. Photographs displaying the face/body at ages 1, 4, and 10 mo, and 1.5 and 3 yr (the time points at which children residing in Japan undergo checkups for development and diseases), as well as at ages ≥ 4 yr, were used to record the phenotypes. Patients were instructed to check records in the Maternal and Child Health Handbook or check with their guardians. This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Kikugawa General Hospital (Kikugawa, Japan). Written informed consent for the publication of clinical details and/or clinical images was obtained from each patient and the parent/guardian/relative of the patient. Given the use of facial/body photographs, measures were taken to protect the identities of all participants.

Results

All cases harbored the p.Met918Thr mutation, and none presented a family history of MEN2B. At the time of the present assessment, the patients (3 males and 3 females) had a median age of 23 (range: 14–31) yr. The median age at MEN2B diagnosis, as determined by cervical masses, oral lesions, enteritis, and other symptoms (Supplementary Table 1), and the time point at which patients underwent thyroidectomy for MTC was 11 (6–19) yr. Patient characteristics are summarized in Table 1. Motor development was delayed to some extent, whereas physique and mental development during infancy were moderate when compared with newborns and infants in Japan (Table 1) (6–9).

During infancy, the patients presented with two new early symptoms (i, ii) and one characteristic symptom (iii) of MEN2B. (i) Although none of the

Table 1. Characteristics of the study participants with multiple endocrine neoplasia type 2B

| Characteristics                                      | Median | Range     | Normal median (ref) |
|------------------------------------------------------|--------|-----------|---------------------|
| Number of participants                               | 6      | 6–36      |                     |
| Age, yr                                              | 23     | 14–31     |                     |
| Sex                                                  | F, 3; M, 3 |         |                     |
| Age at diagnosis of MEN2B, yr                        | 11     | 6–19      |                     |
| Age at diagnosis of MTC, yr                          | 11     | 6–19      |                     |
| Age when any other diseases* were suspected or diagnosed, yr | 2      | 0.125–3   |                     |
| Term at birth, wk                                     | 39.5   | 38–40     | 37–41; 94.0% ‡      |
| Height at birth, cm                                  | 49.0   | 42–52.2   | F, 48.5; M, 49.0(8) |
| Body weight at birth, g                              | 3,267  | 2,294–3,818| F, 2,950; M, 3,000(8)|
| Head circumference at birth, cm                      | 33.7   | 32–35.5   | F, 33.0; M, 33.5(8) |
| Chest circumference at birth, cm                     | 32.5   | 28.5–34   | F, 31.8; M, 32.0(8) |
| Father’s age at birth, yr (n = 5)                    | 32     | 29–40     | No data             |
| Mother’s age at birth, yr (n = 5)                    | 30     | 29–38     | 27.4 (First baby) (8)|
| Delivery method                                      | Vaginal delivery, 3; Cesarean section, 3 | |                     |
| Newborn asphyxia, %                                  | 0      | 0         |                     |
| Hospitalization or scrutiny during the neonatal period †, % | 67     | 65–82.2   | F, 70.5; M, 70.3(8, 9)|
| Height at 10-mo checkup, cm                          | 68.1   | 65.8–72.2 | F, 70.5; M, 70.3(8, 9)|
| Body weight at 10-mo checkup, g                       | 8085   | 7,400–8,810| F, 8,260; M, 8,320(8, 9)|
| Head circumference at 10-mo checkup, cm (n = 5)      | 45     | 36.6–45.2 | F, 44.0; M, 45.3(8, 9)|
| Head control, mo (n = 5)                             | 5      | 4–5       | 4 to 5 # (8)        |
| Rolled over, mo (n = 5)                              | 6      | 6–9       | 6 to 7 # (8)        |
| Took first steps, mo (n = 5)                         | 17     | 16–19     | 15 to 16 # (8)      |
| Spoke first word, mo (n = 5)                         | 12     | 6–17      | 15 to 16 # (8)      |
| Academic background or occupation                    | Student (n = 3), White-collar worker (n = 2), Freelancer (n = 1) | |                     |

F, female; M, male; MEN2B, multiple endocrine neoplasia type 2B; MTC, medullary thyroid carcinoma. * Multiple answers. Other suspected diseases: Hirschsprung disease (n = 4), Williams syndrome (n = 1), Prader–Willi syndrome (n = 1), neuroblastoma (n = 1), and hydronephrosis (n = 1). † Reasons for hospitalization: bloating, poor feeding (n = 3) and jaundice (n = 1). ‡ All births in Japan in 2000/37–41 wk birth in Japan in 2000; 530633/564644. # Pass rate is 90%. † 2000 is the base year of the growth standard for Japanese children.
patients presented neonatal asphyxia or physical issues at birth, four of the six (67%) subjects were hospitalized or subjected to detailed examination as neonates for bloating with poor feeding (3/6) or jaundice (1/6) (Table 2). ii) Three of five subjects born between 1984 and 2003 were positive for neuroblastoma, as screened using high-performance liquid chromatography (HPLC) analysis of urinary vanillylmandelic and homovanillic acids (screening-positive criteria: values above three standard deviations [S.D.] of the mean creatinine concentration in µg/mg). Of the two patients with negative findings, one was tested using a qualitative test, and the result for the other could not be determined using the employed analytical method. Among the three positive patients, one with markedly high urine catecholamine metabolite levels was admitted to the hospital several times after interruption of breastfeeding and underwent scintigraphy, and another patient underwent multiple examinations at the hospital owing to suspected neuroblastoma, but no tumor was found in either case. For the third positive patient, no description was available apart from the HPLC results. These positive patients were also screened for pheochromocytoma during the 3–4-yr period after the MTC surgery, but only one patient developed pheochromocytoma (Table 2) (for details, please refer to Supplementary Table 1). iii) Prior to one year of age, the patients presented with ganglioneuromas (5/6) and bumpy lips or lip ganglioneuromas (3/6). Eventually, changes in bumpy lips (multiple lip neuromas) were noticeable owing to ganglioneuromas or abdominal expansion caused by pseudo-Hirschsprung disease, which were most often resulted in the patients presenting with ganglioneuromas (Table 2).

Table 2. Frequency of each feature or symptom

| Feature or symptom                        | Age 0–1 n (%) | Age 0–2 n (%) | Age 0–5 n (%) | All terms n (%) |
|------------------------------------------|---------------|---------------|---------------|----------------|
| Ganglioneuromas                          | 5 (83)        | 6 (100)       | 6 (100)       | 6 (100)        |
| Ganglioneuromas without bumpy lips       | 2 (33)        | 2 (33)        | 2 (33)        | 6 (100)        |
| Lip ganglioneuromas, bumpy lips          | 3 (50)        | 4 (67)        | 5 (83)        | 5 (83)         |
| Tongue ganglioneuromas                   | 1 (17)        | 1 (17)        | 2 (33)        | 6 (100)        |
| Intestinal ganglioneuromatosis           | 1 (17)        | 1 (17)        | 1 (17)        | 3 (50)         |
| Eyelid or conjunctival ganglioneuromas   | 0 (0)         | 0 (0)         | 0 (0)         | 2 (33)         |
| Severe constipation or pseudo-Hirschsprung disease | 4 (67)        | 4 (67)        | 4 (67)        | 5 (83)         |
| Motor or muscle weakness (hypotonia)     | 4 (67)        | 4 (67)        | 4 (67)        | 4 (67)         |
| Neuroblastoma screening-positive (n = 5) | 3 (60)        | 3 (60)        | 3 (60)        | 3 (60)         |
| Screening by VMA spot test (1984–1989)   | 0/1 (0)       | 0/1 (0)       | 0/1 (0)       | 0/1 (0)        |
| Screening by VMA spot test or HPLC (1989–1990) | 0/1 (0)       | 0/1 (0)       | 0/1 (0)       | 0/1 (0)        |
| Screening by HPLC (1990–2003)            | 3/3 (100)     | 3/3 (100)     | 3/3 (100)     | 3/3 (100)      |
| Suckling disorder                        | 3 (50)        | 3 (50)        | 3 (50)        | 3 (50)         |
| Alacrima                                  | 2 (33)        | 2 (33)        | 3 (50)        | 4 (67)         |
| Pes cavus                                | 2 (33)        | 2 (33)        | 2 (33)        | 4 (67)         |
| Eating disorder                          | 1 (17)        | 1 (17)        | 1 (17)        | 1 (17)         |
| Failure to thrive (neonatal)             | 1 (17)        | 1 (17)        | 1 (17)        | 1 (17)         |
| Chronic intestinal pseudo-obstruction    | 0 (0)         | 1 (17)        | 1 (17)        | 2 (33)         |
| Corneal hypertrophy                      | 0 (0)         | 0 (0)         | 1 (17)        | 1 (17)         |
| Kidney anomalies                         | 0 (0)         | 1 (17)        | 1 (17)        | 1 (17)         |
| Medullary thyroid carcinoma              | 0 (0)         | 0 (0)         | 0 (0)         | 6 (100)        |
| Marfanoid habitus                        | 0 (0)         | 0 (0)         | 0 (0)         | 5 (83)         |
| High-arched foot                         | 0 (0)         | 0 (0)         | 0 (0)         | 3 (50)         |
| Pheochromocytoma                         | 0 (0)         | 0 (0)         | 0 (0)         | 3 (50)         |
| Intestinal paresis                       | 0 (0)         | 0 (0)         | 0 (0)         | 1 (17)         |
| Scoliosis                                | 0 (0)         | 0 (0)         | 0 (0)         | 1 (17)         |
| Achalasia or gastroparesis               | 0 (0)         | 0 (0)         | 0 (0)         | 0 (0)          |
| Pectus excavatum                         | 0 (0)         | 0 (0)         | 0 (0)         | 0 (0)          |
| Cleft hand                               | 0 (0)         | 0 (0)         | 0 (0)         | 0 (0)          |
| Common personality among participants    | Unknown       | Unknown       | Unknown       | 5 (83)         |
| Perseverant                              | Unknown       | Unknown       | Unknown       | 3 (50)         |
| Kind                                     | Unknown       | Unknown       | Unknown       | 3 (50)         |
| Cheerful                                 | Unknown       | Unknown       | Unknown       | 3 (50)         |
| Own pace                                 | Unknown       | Unknown       | Unknown       | 2 (33)         |

Other features extracted from the free description. No common symptoms between the participants and symptoms that had not been reported previously as characteristic features of MEN2B (age): submucosal cleft palate (3 mo), cleft uvula (3 mo), velopharyngeal incompetence (3 mo), apnea (4 mo), adrenomedullary hyperplasia (6 mo), Arnold–Chiari deformity (9 mo), spina bifida (9 mo), hypoglycemia (1 year), neurogenic bladder (1 yr 11 mo), pes valgus (2 yr), joint hypermobility (2 yr), short stature (3 yr 3 mo), metabolic acidosis (3 yr 6 mo), retracted testicle (3 yr 10 mo), tooth malalignment (unknown), cholecystitis (7 yr), cataract (17 yr), dolichocephaly (20 yr), nostril ganglioneuromas (31 yr), and laryngopharynx ganglioneuromas (31 yr). VMA, vanillylmandelic acid; HPLC, high-performance liquid chromatography.
observed before one year of age (Fig. 1). Patient 1 was suspected of having Williams syndrome characterized by thick lips, based on the facial appearance at two years of age (this symptom was classified as appearing at that age). Patients 2, 3, and 4 presented thick lips before one year of age. Of the two patients presenting no visual evidence (photographs), one reported the appearance of thick lips at three years of age, and the other reported only tongue ganglioneuroma at six months; the latter was concluded to be negative for lip symptoms, despite possible positive manifestations.

All patients were suspected of presenting one or more comorbidities at a median age of 2 (range: 0.125–3) yr, including Hirschsprung disease, Williams syndrome, Prader-Willi syndrome, neuroblastoma, and hydronephrosis, based on severe constipation, facial appearance, and muscle weakness, among other phenotypes. By analyzing only MEN2B characteristic symptoms appearing around 1 yr of age, a median of 3 symptoms (range: 1–5) was estimated. All patients manifested at least one MEN2B characteristic symptom, including bumpy lips or lip ganglioneuromas, ganglioneuromas in parts other than the lips, pseudo-Hirschsprung disease, and alacrima. Furthermore, almost all these characteristic symptoms appearing before the age of five were first detected by one year of age (Table 2).

**Discussion**

Our six patients highlight the possibility of new physical and clinical manifestations that could support the early diagnosis of MEN2B, an ultra-rare disease.

A high frequency of hospitalization during the neonatal period and abdominal expansion may be potential diagnostic phenotypes during infancy. Term babies without any birth complications are seldom hospitalized during the neonatal period. In the present study, severe constipation or pseudo-Hirschsprung disease was observed in 67% (4/6) patients during infancy. In patients with MEN2B, gastrointestinal symptoms occur relatively early, at an average age of 4.5 yr (S.D., 4.3) (10); however, their frequency during infancy remains unknown among Asian populations. In the present study, the prevalence of abdominal symptoms in Japanese infants was similar to that reported by Brauckhoff et al. (5). Numerous patients with MEN2B present with megacolon (10); however, owing to a lack of X-ray investigation data, we could not confirm whether patients exhibited megacolon during the neonatal period or infancy unless diagnosed by a doctor. The prevalence of hyperbilirubinemia in Asian neonates is reportedly high (9.7%) (11). Hospitalization due to jaundice might have been incidental; however, as poor enterohepatic circulation due to constipation is one underlying cause of jaundice, it is unclear from the case report whether the symptoms are related to MEN2B. As neonatal jaundice is a subject of close examination, we included it as a neonatal admission.

![Fig. 1. Photographic records of patients with MEN2B included in this study at ages 0–5 yr. The patients exhibited changes in bumpy lips (multiple lip neuromas), owing to ganglioneuromas, or abdominal expansion caused by pseudo-Hirschsprung disease with severe constipation, most often observed before one year of age. Patient 1 reported bumpy lips, with an unknown time of appearance, in the survey. As Patient 1 was suspected of presenting Williams syndrome characterized by thick lips, based on facial appearance at age 2, this symptom was classified as having appeared at that age. Patient 2 reportedly presented thick lips from age 0 yr. Patients 3 and 4 reportedly presented thick lips from age 0 yr; although Patient 4 also reported this feature, it was speculated by the parents to be within the range of individual differences. Abdominal expansion was also observed. In addition, most parents captured an abdominal picture as they believed that the child’s abdomen was larger than that of other children.](image-url)
Most parents captured an abdominal picture of their child as they felt that the abdomen was larger than that of other children.

Furthermore, facial gestalt may contribute to an early diagnosis. Bumpy lips due to multiple neuromas were a MEN2B-specific symptom observed in > 50% of the patients by 1 yr of age (Table 2); this was in contrast with previously reported rates of 0% (12) and 17% (5) for bumpy lip appearance by 1 yr of age (Table 3). The lip thickness, which was expected to be evident later, was apparent even before one year of age. The most crucial reason for contrasting rates of early symptoms described in previous reports might be attributed to differences in survey methods employed. Our findings were based on photographic records that could have resulted in early symptom reports (from age 0 yr). Thus, machine learning of facial gestalt could be valuable for accurately diagnosing MEN2B even before one year of age, as previously attempted for other syndromes, such as Williams syndrome (13).

Surgical resolution of MTC is complex after age 6, with biochemical and structural remission possible in only 15% of patients diagnosed by 1 yr of age (12). Herein, most extra-endocrine signs appearing by five yr of age were present from the age of one, indicating the possibility of early diagnosis. In this case series, the patients presented with MEN2B at an average age at diagnosis similar to that reported previously (2, 14), which suggests that the severity of “early extra-endocrine symptoms” in these patients may also be average.

Herein, > 60% of patients with MEN2B had suspected neuroblastoma characterized by the production of catecholamines (dopamine, noradrenaline, and adrenaline), metabolites of which were screened during infancy, a previously unreported phenomenon that may represent a new early symptom of MEN2B.

Table 3. Comparison of the proportion (%) of early phenotypes or symptoms in the first year of life with those in previous reports

| Phenotypes or symptom                | Brauckhoff et al. (5) (n = 25) | Redlich et al. (12) (n = 24) | Present study (n = 6) |
|--------------------------------------|---------------------------------|-----------------------------|----------------------|
|                                      | Germany                         | Germany                      | Japan                |
|                                      | Retrospective case-control study, Hospital-based, Questionnaire/ face-to-face or telephone interview. | Retrospective, multicenter registry study (Estimate from Kaplan–Meier curve). | Retrospective case series, MEN alliance-based, a questionnaire with maternal handbook and photographic records. |
| Feeding problems                     | 46                              | 4                           | 50                   |
| Frequent flatulence                  | 33                              | Uncertain                    | 50 (neonatal)        |
| Tearless crying                      | 86                              | 0                           | 33                   |
| Constipation                         | 61                              | 30                          | 67                   |
| Conjunctivitis                       | 24                              | 0                           | 0 (no one listed this symptom) |
| Foot abnormalities                   | 30                              | 8                           | 0                    |
| Joints or motor weakness             | 19                              | Uncertain                    | 67                   |
| Bumpy lips                           | 17                              | 0                           | 50                   |
| Intraoral neuroma                    | 17                              | 4                           | 17                   |
| Neuroblastoma screening-positive     | Uncertain                       | Uncertain                    | 60                   |
whether positive-screening for infantile neuroblastoma is an early phenotype.

**Conclusion**

The possibility of a new early extra-endocrine phenotype for MEN2B diagnosis was identified, including neonatal hospitalization and positive neuroblastoma on mass screening. In addition, early extra-endocrine phenotypes in infancy, as reported previously, were confirmed in Japanese children.

**Conflict of interests:** None declared.

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