Natural course of MEN-2B syndrome in a Dutch single-center cohort

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Background

Multiple endocrine neoplasia type-2B (MEN-2B) is a rare endocrine disease associated with early and aggressive medullary thyroid carcinoma (MTC), pheochromocytoma and several non-endocrine manifestations[1-3].

MEN-2B is often diagnosed late, when symptomatic thyroid disease is present[3].

Recognition of early, often non-endocrine, manifestations is elemental and may lead to early intervention through early diagnosis[1-4]. However, early recognition is complicated by both the broad clinical spectrum of manifestations and rareness of MEN-2B.

Objective

The aim of this study is to describe disease presentation, subsequent manifestations and outcome in a MEN-2B cohort and to aid in increasing awareness for early symptoms.

Methods

A retrospective single-center cohort study was conducted at the University Medical Center Utrecht, a tertiary referral and national expertise-center for MEN-patients.

All MEN-2B patients in follow-up between 1990-2017 were included and medical records were reviewed.

Table 1: Patient characteristics and different manifestations of MEN-2B

Case	Sex	Age at Dx (yr)	Follow-up duration (yr)	Presenting symptom(s)	Thyroid at Dx	Pheo*
1	F	0.1	9.8	GI problems	CCH	No
2	F	6.5	0.5	Unexplained DMD, MW, HT, WES	MTC	No
3	F	0.3	4.7	GI problems	CCH	No
4	M	0.1	3.6	GI problems	MTC	No
5	F	16	3.5	Cheek NR, neck lump	MTC	No
6	M	12	11	DMD, MW, HT, oral NRs, CaL	MTC	No
7	F	6.0	27	DMD, GI problems, dysmorphia (NR)	CCH †	Yes
8	M	16	38	GR	MTC	Yes

*Table 1. Patient characteristics and different manifestations of MEN-2B. Abbreviations: F= female, M= male. Dx= diagnosis, yr= year(s). GI = gastro-intestinal, DMD= delayed motor development, MW= muscle weakness, HT=hypotonia, NR= neuroma, CaL= Café au lait spot, GR = growth retardation, CCH= C-cell hyperplasia, MTC = medullary thyroid carcinoma, Pheo = pheochromocytoma, WES = whole exome sequencing. * Anytime during follow-up. † Possible MTC.*

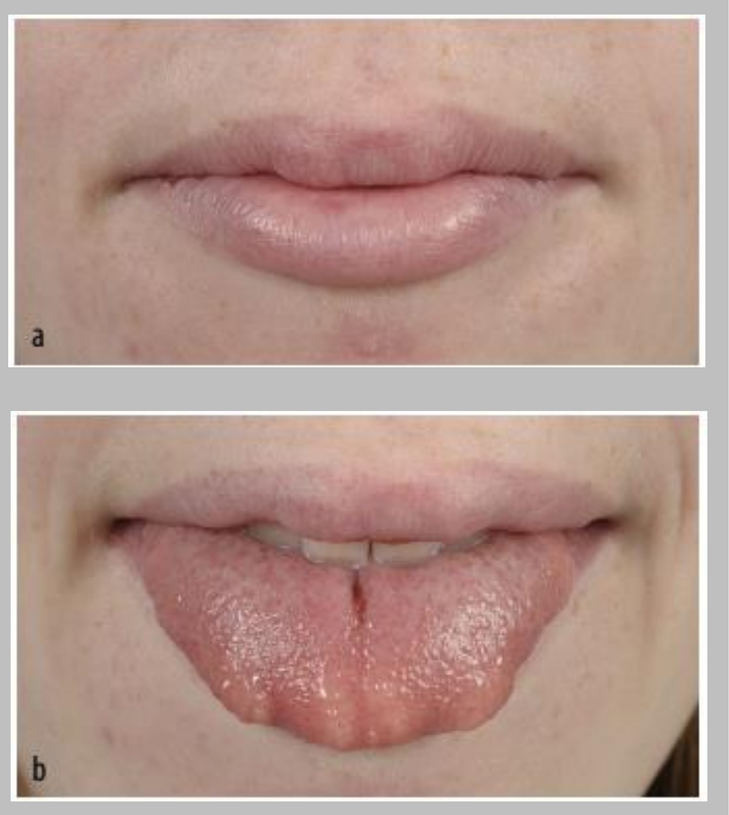

Figure 1. Phenotypical characteristics of MEN-2B. A. Hypertrophic bumpy lips. B. Oral neuromas on the tongue (printed with the patient's permission)[5"].

Results

Eight patients (3 males, 5 females) were identified, all had a de novo RET-mutation (Met918Thr). MEN-2B in this cohort most often presented with neonatal gastro-intestinal symptoms (50%), as well as with mucosal neuromas (38%) or delayed motor development (38%); not with symptomatic MTC. For detailed patient characteristics and different manifestations: see table 1.

Thyroidectomy cured or prevented thyroid disease in 50% of patients. Patients operated at young age (<1 year) have remained free of disease. Pheochromocytoma was detected in 2; the youngest patient presenting at an age of 16 years. Of note: pheochromocytoma incidence may be underestimated by the relative young current age of patients included in this cohort.

All patients suffered from intestinal problems, most commonly severe and chronic obstipation which severely impacts daily life. Other common non-endocrine manifestations, which might help to raise suspicion of MEN-2B, were oral and ocular neuromas, 'hypertrophic bumpy lips' (see Figure 1), central diastemas as well as less specific symptoms such as joint hyperlaxity and a marfanoid body habitus. Furthermore, literature[1] reports alacrimia in the majority of patients with MEN-2B; we have thus far not systematically performed ophthalmologic evaluation in the reported cohort.

Conclusion

Awareness among clinicians of symptoms of MEN-2B is important, as early diagnosis of MEN-2B is associated with still curable thyroid disease. Neonatal gastro-intestinal manifestations may offer a window of opportunity for early detection of MEN-2B, as rectal biopsies can show diffuse intestinal ganglioneuromatosis, strongly pointing to a diagnosis of MEN-2B. In addition, other non-endocrine manifestations can be the first detectable sign of MEN-2B. Therefore, these symptoms are important to recognize as they can be the clue for an early diagnosis of MEN-2B.

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