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Phenotypic Spectrum of SBF2 Mutations

Josef Finsterer, MD, PhD[1], Sinda Zarrouk-Mahjoub, PhD[2]

[1]Krankenanstalt Rudolfstiftung, Vienna, Austria.

[2]University of Tunis El Manar and Genomics Platform, Pasteur Institute of Tunis, Tunisia.

fifigs1@yahoo.de

***Corresponding Author:** Finsterer J, MD, PhD, Krankenanstalt Rudolfstiftung, Vienna, Austria, Europe.*

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Letter to the Editor

We read with interest the article by Lassuthova et al. about 10 patients from 7 families with Charcot-Marie-Tooth disease type 4B2 (CMT4B2) carrying nine different mutations in the *SBF2* gene [1]. We have the following comments and concerns.

Patients with CMT4B2 may not only manifest with autosomal recessive demyelinating sensorimotor neuropathy and early-onset glaucoma, but also with thrombocytopenia [2], fair coloured hair and skin [2], pes cavus [3], or hammertoes [3] (table 1). Were any of these phenotypic features present in any of the probands investigated? Were there any family members without neuropathy but thrombocytopenia or fair coloured skin or hair?

The description of the sensory deficits is misleading. The authors state that none of the patients complained about sensory abnormalities. On clinical neurologic exam, however, mild sensory deficits were found in 7 patients [1]. How do the authors explain that none of the 10 patients complained about sensory deficits but seven had an abnormal sensory testing? Did any of the patients with sensory deficits report frequent pressure palsies, or sensory deficits after forced alcohol consumption or generalised anesthesia? Unfortunately, details about the sensory nerve conduction studies were not reported. Were sensory nerve conduction studies abnormal in all 7 patients with abnormal sensory findings on clinical exam?

The authors mention that nerve biopsy was taken previously for diagnostic purposes [1], Were nerve biopsies taken from motor, sensory, or from mixed nerves? In case only sensory nerves were biopsied, did the neuropathological findings correlate with the findings of sensory nerve testing on clinical exam or with nerve conduction studies? Were there patients with normal exam but abnormal biopsy and vice versa? How many patients altogether underwent nerve biopsy? The authors report loss of myelinated axons [1]. Thus, there was not only demyelination but also axonal damage. Was axonal loss classified as primary or secondary?

It is contradictory to state that nine patients had involvement of the lower limbs muscles and to mention that three patients had normal distal muscle functions and bulk [1]. Do the authors mean weakness, wasting, or fasciculations? Did any of the 10 patients undergo needle-electromyography? Were fibrillations or fasciculations, prolonged motor unit action potential duration, or a sparse interference pattern recorded in any patient? Did any of the 10 patients undergo muscle biopsy?

The authors found a visual problem in four of their patients [1]. It should be specified what is meant by "vision problem". Was visual acuity reduced, was there double vision, were there visual field defects, was there blurred vision? Clarification of this point is crucial as different causes can be responsible for a visual problem, such as optic atrophy, macular degeneration, retinopathy, or a choroidal defect? Was there glaucoma in these four patients? Was visual impairment truly a manifestation of the *SBF2* mutation? Did those with glaucoma manifest with visual impairment?

Hearing impairment is not well appreciated in the literature as a manifestation of *SBF2* variants [4]. According to figure 1H, about 20% of the patients had hearing impairment. How many of the 10 patients had in fact impaired hearing and how many in the literature?

Concerning the manifestations at onset, foot deformity should not be specified as "symptom" unless it caused pain or abnormal sensation.

Table 1. *Phenotypic manifestations of SBF2 carriers*

Item	Current cohort	literature
Demyelinating neuropathy of LL	x	x
Demyelinating neuropathy of UL	x	x
Glaucoma	x	x
Claw hand defect	x	x
Scoliosis	x	?
Hypophonia	x	no
Hypoacusis	x	no
Pes cavus	no	x
Hammertoes	no	x
Thrombocytopenia	no	x
Fair coloured skin/hair	no	x

Conclusion

This retrospective study could be more meaningful if the number of patients who underwent a specific instrumental investigation and those with an abnormal result would have been provided. Since CMT4B2 is a motor and sensory neuropathy, it is crucial to provide results of sensory nerve conduction studies. Lacking is also a discussion of recently reported phenotypic features in *SBF2* carriers. As long as precise figures are not presented, more uncertainty than solution of unsolved issues may be produced.

Author's Contribution

JF: design, literature search, discussion, first draft, SZM: literature search, critical review

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