to elevated levels of porphyrin metabolites rather than a direct effect on peripheral nerve function.

In conclusion, our study has provided novel insights into the pathophysiology of acute lead neuropathy. The data suggest that lead intoxication may result in acute axonal depolarization, possibly due to impairment of the energy-dependent axonal Na^+/K^+ pump. It has also been demonstrated that early diagnosis and institution of chelation treatment may result in clinical and neurophysiological improvement.

This study was supported by a Career Development Award from the National Health and Medical Research Council of Australia (568680 to A.K.) and by an Australian Postgraduate Award (to S.P.).

REFERENCES

1. Rubens O, Logina I, Kravale I, Eglite M, Donaghy M. Peripheral neuropathy in chronic occupational inorganic lead exposure: a clinical and electrophysiological study. J Neurol Neurosurg Psychiatry 2001;71:200–204.
2. Thomson RM, Parry GJ. Neuropathies associated with excessive exposure to lead. Muscle Nerve 2006;33:732–741.
3. Oh SJ. Lead neuropathy: case report. Arch Phys Med Rehabil 1975; 56:312–317.
4. Krishnan AV, Lin CS, Park SB, Kiernan MC. Assessment of nerve excitability in toxic and metabolic neuropathies. J Peripher Nerv Syst 2008;13:7–26.
5. Chanez C, Giguere JF, Flexor MA, Bourre JM. Effect of lead on Na+,K+ATPase activity in the developing brain of intra-uterine growth-retarded rats. Neurochem Pathol 1986;5:37–49.
6. Kiernan MC, Burke D, Andersen KV, Bostock H. Multiple measures of axonal excitability: a new approach in clinical testing. Muscle Nerve 2000;23:399–409.
7. Huynh W, Krishnan AV, Lin CSY, Vucic S, Kiernan MC. The effects of large artery ischemia and subsequent recanalization on nerve excitability. Muscle Nerve 2011;44:841.
8. Kiernan MC, Bostock H. Effects of membrane polarization and ischemia on the excitability properties of human motor axons. Brain 2000;123:2542–2551.
9. Maiti AK, Saha NC, Paul G. Effect of lead on oxidative stress, Na+K+ATPase activity and mitochondrial electron transport chain activity of the brain of *Clarias batrachus*. Bull Environ Contam Toxicol 2010;84:672–676.
10. Krishnan AV, Lin CS, Kiernan MC. Excitability differences in lower-limb motor axons during and after ischemia. Muscle Nerve 2005;31:205–213.
11. Han SE, Boland RA, Krishnan AV, Vucic S, Lin CS, Kiernan MC. Ischemic sensitivity of axons in carpal tunnel syndrome. J Peripher Nerv Sys 2009;14:190–200.
12. Windebank AJ, McCall JT, Hunder HG, Dyck PJ. The endoneurial content of lead related to the onset and severity of segmental demyelination. J Neuropathol Exp Neurol 1980;39:692–699.
13. Bostock H, Baker M, Grafe P, Reid G. Changes in excitability and accommodation of human motor axons following brief periods of ischemia. J Physiol (Lond) 1991;441:513–535.
14. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Ischemia induces paradoxical changes in axonal excitability in end-stage kidney disease. Brain 2006;129:1585–1592.
15. Lin CS, Krishnan AV, Lee MJ, Zagami AS, You HL, Yang CC, et al. Nerve function and dysfunction in acute intermittent porphyria. Brain 2008;131:2510–2519.
16. Straka JG, Rank JM, Bloomer JR. Porphyria and porphyrin metabolism. Ann Rev Med 1990;41:457–469.
17. Albers JW, Fink JK. Porphyric neuropathy. Muscle Nerve 2004;30: 410–422.
18. Hernberg S, Nikkanen J. Enzyme inhibition by lead under normal urban conditions. Lancet 1970;1:63–64.
19. Russell VA, Lamm MC, Taljaard JJ. Inhibition of Na+, K+-ATPase activity by delta-aminolevulinic acid. Neurochem Res 1983;8:1407–1415.
20. Becker DM, Goldstuck N, Kramer S. Effect of delta-aminolaevulinic acid on the resting membrane potential of frog sartorius muscle. S Afr Med J 1975;49:1790–1792.
21. Becker D, Viljoen D, Kramer S. The inhibition of red cell and brain ATPase by delta-aminolaevulinic acid. Biochim Biophys Acta 1971;225: 26–34.

AXONAL NEUROPATHY, LONG LIMBS, AND BUMPY TONGUE: THINK OF MEN2B

ANA M. RAMOS-LEVÍ, MD,[1] ÁNGEL DÍAZ-PÉREZ, MD, PhD,[1] MARÍA-JESÚS SOBRIDO, MD, PhD,[2] SERGIO PIÑEIRO-HERMIDA, BSc,[3] PATRICIA BLANCO-ARIAS, PhD,[2] JOSÉ M. CABEZAS-AGRÍCOLA, MD,[4] SAMUEL I. PASCUAL-PASCUAL, MD,[5] and DAVID ARAÚJO-VILAR, MD, PhD[4]

[1] Division of Endocrinology, Metabolism and Nutrition, Hospital Universitario Clínico San Carlos, Madrid, Spain
[2] Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, Spain
[3] Grupo de Medicina Xenómica, University of Santiago de Compostela and Center for Network Research on Rare Diseases (CIBERER), Institute of Health Carlos III, Spain
[4] Division of Endocrinology and Nutrition, Hospital Clínico Universitario de Santuago de Compostela, Tv Choupana s/n, 15706 Santiago de Compostela, Spain
[5] Division of Neuropediatrics, Hospital Universitario La Paz, IDIPAZ, Madrid, Spain

Accepted 15 May 2012

ABSTRACT: *Introduction:* Multiple endocrine neoplasia type 2 (MEN 2) is an uncommon autosomal dominant cancer syndrome which can be associated with nerve conduction abnormalities. *Methods:* A 14-year-old boy with a family history of consanguinity developed progressive gait clumsiness, pes cavus, hypotonia, and mucosal tumors of the lips and tongue since the age of 3 years. At age 11 years, he was diagnosed with an hereditary motor neuropathy (Charcot-Marie-Tooth syndrome). *Results:* Physical examination revealed a Marfanoid habitus, mucocutaneous verrucous tumors, thyroid nodules, and cervical adenopathy. Genetic testing demonstrated the p.M918T mutation in the *RET* gene, and blood tests showed elevated levels of calcitonin. *Conclusions:* Clinical suspicion in MEN2 is crucial for early diagnosis and subsequent therapy. Mucosal neuroma and a Marfanoid habitus are especially useful. Other neurologic manifestations should not disguise the endocrine disorder, because early diagnosis and treatment of medullary thyroid carcinoma determines the prognosis.

Muscle Nerve **46:** 961–964, 2012

Abbreviations CMAP, compound muscle action potential; CMT, Charcot-Marie-Tooth syndrome; DEXA, Dual Energy X-ray Absorbtiometry; ENMG, Electroneuromiographic examination; FMTC, familial medullary thyroid carcinoma; MEN2B, Multiple Endocrine Neoplasia type 2; MTC, medullary thyroid carcinoma

Key words: axonal neuropathy; Charcot-Marie-Tooth syndrome; medullary thyroid carcinoma; MEN 2B; RET

Correspondence to: D. Araújo-Vilar; e-mail: david.araujo@usc.es

Published online 22 May 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.23466

Multiple endocrine neoplasia type 2 (MEN 2) is an uncommon autosomal dominant cancer syndrome (estimated prevalence 1/30,000), with

complete penetrance but variable expressivity.[1] There are 3 distinct clinical subtypes - MEN 2A, familial medullary thyroid carcinoma (FMTC), and MEN 2B. The major components are medullary thyroid carcinoma (MTC), pheochromocytoma, and primary hyperparathyroidism.[2] The MEN 2 syndrome is caused by germline mutations in the *RET* proto-oncogene.

The most aggressive variant is subtype 2B, which is characterized by developmental alterations such as multiple mucocutaneous neurofibromas, ganglioneuromatosis of the gastrointestinal tract, muscle and skeletal abnormalities, and ophthalmic alterations.[3] MEN 2B patients develop a more aggressive form of MTC, with high morbidity and mortality rates. Approximately 95% of MEN 2B patients have the p.M918T *RET* mutation, and more than 50% of the cases are a *de novo* germline mutation.[1,4] Due to the poor prognosis of MTC in MEN 2B, diagnosis must not be delayed. Certain clinical manifestations, especially mucosal neuroma, should alert the clinician to the diagnosis, even though the association of other neurologic manifestations may disguise the endocrine disorder. This occurred in the unusual patient that we describe.

CASE REPORT

A 14-year-old boy with a family history of consanguinity (parents were second cousins) was referred to our hospital with the suspicion of Berardinelli-Seip syndrome (congenital generalized lipodystrophy), which was ruled out in the initial clinical exam.

Since the age of 3 years, he had developed progressive clumsiness of gait, pes cavus, muscle hypotonia and frequent falls, together with bumpy lips, mucosal tumors of the tongue, hypertelorism, and mandibular divergence. At age 11 years, he was diagnosed with a sensory-motor hereditary neuropathy (Charcot-Marie-Tooth, CMT syndrome) based on the following clinical findings: fibular atrophy, pes cavus, hammer toes, Achilles tendon retraction (Fig. 1A), foot extensor weakness, and mild decrease of distal vibratory sense. Electroneuromyographic examination (ENMG) showed a neurogenic pattern in the extensor digitorum brevis muscle and low CMAP amplitudes in the fibular nerves, with normal motor and sensory nerve conduction velocities. Because his mother had pes cavus (Fig. 1B), the diagnoses of CMT2 and CMTX were entertained, however, her ENMG was normal. Molecular genetic screening for the following CMT genes disclosed no mutations in the patient: *LMNA, GJB1, BSCL2, HSPB1, HSPB2, MPZ*, and *MFN2*. He grew tall rather quickly with little body weight gain and began puberty when he was 12. He improved his gait with rehabilitation techniques. A few months before being referred to our hospital he had noticed the appearance of several neck tumors.

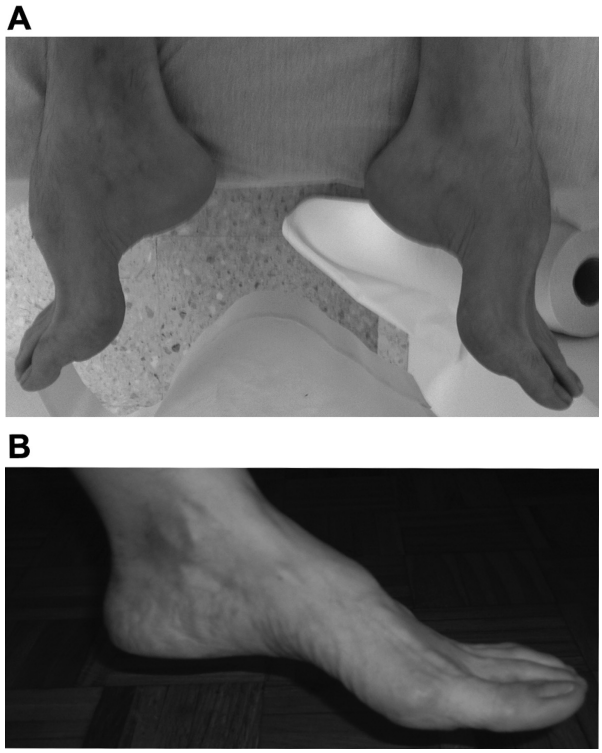

FIGURE 1. (A) Photograph of the patient's feet showing pes cavus, tendon retraction and hammer toes. **(B)** Photograph of the patient's mother's foot showing pes cavus.

In addition to the neurological findings, physical examination revealed a Marfanoid body habitus, scoliosis, hypertelorism, low-set ears, thick and prominent lips, macroglosia and several verrucous tumors on the tips and borders of the tongue, which were attributed to repeated trauma (Fig. 2). Neck palpation allowed the identification of a 2-cm thyroid nodule and multiple small painful adenopathies. Pubertal development was Tanner stage III, with 12 ml testes. His weight was 43 kg, height was 179.5 cm, body mass index (BMI) was 13.3 kg/m^2, body fat was 10.2% (4.3 kg) (evaluated by DEXA), blood pressure was 101/60 mmHg, and heart rate was 55 bpm. Because clinical data suggested the possibility of MEN 2B, the *RET* proto-oncogene was tested, and the patient was found to be heterozygous for the NM_020975.4:c.2753T>C (p.Met918Thr) mutation, which was absent in both parents.

Blood tests revealed the following: calcium 10.3 mg/dl, phosphorus 4.8 mg/dl, TSH 2.59 uIU/ml, T4L 9.34 pg/ml. Urine catecholamines and metanephrines were negative. He had high levels of carcinoembryonic antigen (15.4 ng/ml [0.1–10]) and calcitonin (2408 pg/ml [0–20]). Levels of chromogranin-A (12.5 nmol/ml [<100]) and PTHi (31 pg/ml) were normal.

Neck ultrasonography showed a 4-cm mass in the inferior margin of the left thyroid lobule, suggesting a primary thyroid neoplasm. Multiple

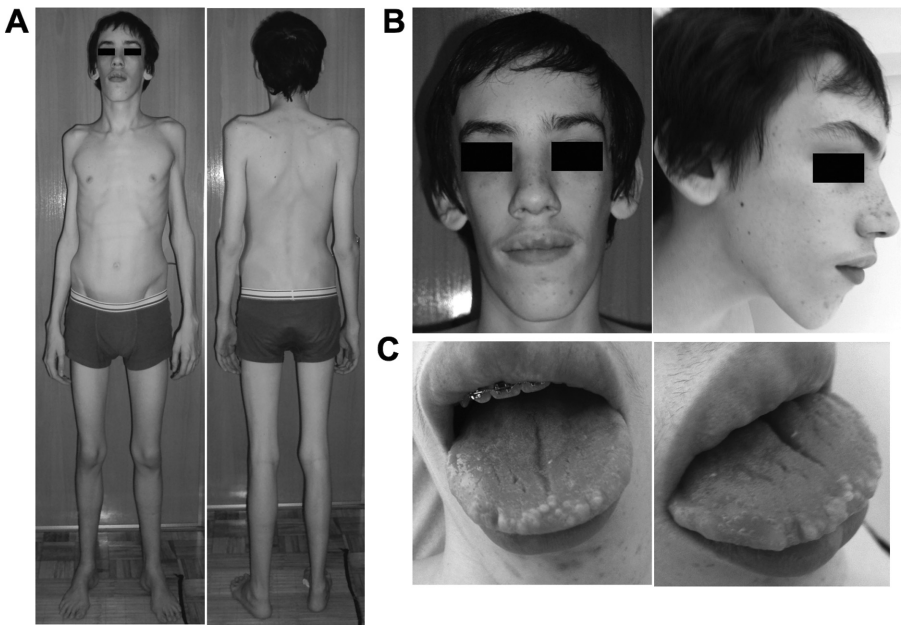

FIGURE 2. (A) Whole-body photograph showing the patient's Marfanoid body habitus, with long and thin limbs and joint hyperlaxity. **(B)** Hypertelorism, low-set ears, thick and prominent lips, and mandibular divergence. **(C)** Macroglosia and several verrucous tumors on the tips and borders of the tongue.

cervical adenopathy was also identified. Total body computerized axial tomography showed the thyroid nodules and adenopathy, but it ruled out other neoplasic localizations.

Based on the features described, we diagnosed the patient with MEN 2B. The presence of MTC with cervical lymphadenopathy was strongly suspected, so after ruling out concomitant pheochromocytoma, the patient underwent total thyroidectomy with bilateral neck dissection.[5] The pathology of the surgical specimens revealed multifocal MTC with lymphovascular invasion and background C-cell hyperplasia (stage IVa). On post-thyroidectomy follow-up 3 months later, the patient had normal calcium and PTH levels and no vocal cord dysfunction. However, although follow-up imaging did not reveal residual disease, calcitonin levels remained elevated at over 150 pg/mL, suggesting the possibility of a less favorable prognosis.[6]

DISCUSSION

The MEN 2B syndrome accounts for approximately 5% of all cases of MEN 2[7] and is characterized by the onset of the MTC at an earlier age, pheochromocytomas in 40–50% of patients, and developmental abnormalities, including mucosal, skin, muscle, skeletal, and ophthalmic, conferring a distinctive phenotype. It is caused by germline mutations in the *RET* proto-oncogene, which encodes a tyrosine kinase receptor necessary for growth differentiation signals in tissues derived from the neural crest. Most cases of MEN 2B are due to the p.Met918Thr mutation in exon 16,[1] which was found in our patient. This mutation is associated with a high risk of aggressive MTC occurring at a younger age, early lymphadenopathy and development of mucocutaneous neuromas.[8,9]

Physical examination played a crucial role in our patient. A Marfanoid habitus, neurofibromas and neck tumors raised the suspicion of MEN 2B syndrome. These phenotypic abnormalities, which usually develop at birth or around ages 1 to 2 years, are early diagnostic clues.[10,11] Although fibular atrophy is a frequent finding in MEN 2B, few cases have been reported with thorough ENMG examination, and there have been no extensive studies on the associated neuropathy. We believe that in this patient the attention drawn by the neuromuscular symptoms since his preschool age, together with the fact that his mother had pes cavus, led to extensive studies to rule out a form of CMT while underscoring other features such as feeding difficulties, early constipation, lack of tearing, and developmental abnormalities.

No mutations were identified in 5 CMT genes in this patient. Numerous genes have been associated with hereditary polyneuropathy,[12] and investigation of additional ones is still ongoing. We cannot rule out that another as yet unidentified mutation could be responsible for the polyneuropathy in this patient, and thus that both entities, MEN 2B and CMT, coexist; the presence of consanguinity in the patient's family history may favor this hypothesis.

However, because neurophysiologic signs of neuropathy were ruled out in the mother, and there was no other family history of neuromuscular disorders, we believe that the neuropathy in this case is more likely part of the MEN 2B syndrome.

Fibular atrophy, scoliosis, pes cavus, and axonal neuropathy have been reported within the phenotypic spectrum caused by RET mutations, due to alterations in mesodermal development.[13] Nerve conduction abnormalities have been described in MEN 2B patients,[14] probably as a result of the variable genotypic expressivity. Involvement of the autonomic nervous system as well as somatic motor and sensory neurons has been recognized, possibly due to the presence of neuromas either macroscopically visible or not.[14] Pathologic involvement of the posterior columns of the spinal cord, which has been described in postmortem examination,[14] may explain the sensory manifestations.

In summary, this case emphasizes the need to carefully look for the cardinal features of MEN 2B in cases with early-onset peripheral axonal neuropathy, even if there is no family history of endocrine tumors. MEN 2B is characterized by an aggressive form of MTC, and early thyroidectomy is essential. This patient had the most common p.Met918Thr mutation and, as in over 50% of the cases,[15] the mutation arose *de novo*. Genetic confirmation of MEN 2B is crucial for subsequent therapy and follow-up, as well as for genetic counseling.

We thank the patient's parents for providing authorization for the publication of the disguised photographs and the genetic information. This study was partially supported by a grant from the Consellería de Innovación, Xunta de Galicia (07CSA017228PR) and the Instituto de Salud Carlos III and European Regional Development Fund, FEDER (PI081449). The authors declare that no competing financial interests exist.

REFERENCES

1. Frank-Raue K, Rondot S, Raue F. Molecular genetics and phenomics of RET mutations: impact on prognosis of MTC. Mol Cell Endocrinol 2010;322:2–7.
2. Wohllk N, Schweizer H, Erlic Z, Schmid KW, Walz MK, Raue F, et al. Multiple endocrine neoplasia type 2. Best Pract Res Clin Endocrinol Metab 2010;24:371–387.
3. Lee NC, Norton JA. Multiple endocrine neoplasia type 2B – genetic basis and clinical expression. Surg Oncol 2000;9:111–118.
4. Moline J, Eng C. Multiple endocrine neoplasia type 2. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993-1999 September 27 [updated 2010 May 04].
5. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565–612.
6. Barbet J, Campion L, Kraeber-Bodere F, Chatal JF. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab 2005;90:6077–6084.
7. Pezckowska M, Januszewizc A. Multiple endocrine neoplasia type 2. Fam Cancer 2005;4:25–36.
8. Yip L, Cote GL, Shapiro SE, Ayers GD, Herzog CE, Sellin RV, et al. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003;138:409–416.
9. Zenaty D, Aigrain Y, Peuchmaur M, Philippe-Chomette P, Baumann C, Cornelis F, et al. Medullary thyroid carcinoma identified within the first year of life in children with hereditary multiple endocrine neoplasia type 2A (codon 634) and 2B. Eur J Endocrinol 2009;160:807–813.
10. Lee MJ, Chung KH, Park JS, Chung H, Jang HJ, Kim JW. Multiple endocrine neoplasia type 2B: early diagnosis by multiple mucosal neuroma and its DNA analysis. Ann Dermatol 2010;22:452–455.
11. Sánchez C, Martínez P, Moreno A, Santiago P, Ramírez FJ, LuqueR. Un nuevo caso de NEM 2B. Endocrinol Nutr 2005;52:139–142.
12. Patzcó A, Shy ME. Update on Charcot-Marie-Tooth disease. Curr Neurol Neursci Rep 2011;11:78–88.
13. Carney JA, Bianco AJ Jr, Sizemore GW, Hayles AB. Multiple endocrine neoplasia with skeletal manifestations. J Bone Joint Surg Am 1981;63:405–410.
14. Dyck PJ, Carney JA, Sizemore GW, Okazaki H, Brimjoin WS, Lambert EH. Multiple endocrine neoplasia type 2b: phenotype recognition; neurological features and their pathological basis. Ann Neurol 1979;6:302–314.
15. Carlson KM, Bracamontes J, Jackson CE, Clarck R, Lacroix A, Wells SA, et al. Parent-of-origin effects in multiple endocrine neoplasia type 2B. Am J Hum Genet 1994;55:1076–1082.

IMPACT OF AGING ON THE PROGRESSION OF NEUROPATHY AFTER LIVER TRANSPLANTATION IN TRANSTHYRETIN Val30Met AMYLOIDOSIS

HARUKI KOIKE, MD, PhD,[1] RINA HASHIMOTO, MD,[1] MINORU TOMITA, MD,[1] YUICHI KAWAGASHIRA, MD, PhD,[1] MASAHIRO IIJIMA, MD, PhD,,[1] TOMOHIKO NAKAMURA, MD, PhD,[1] HIROHISA WATANABE, MD, PhD,[1] HIDEYA KAMEI, MD, PhD,[2] TETSUYA KIUCHI, MD, PhD,[2] and GEN SOBUE, MD, PhD[1]

[1] Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan
[2] Department of Transplantation Surgery, Nagoya University Hospital, Nagoya, Japan

Accepted 29 May 2012

ABSTRACT: *Introduction*: Information related to the long-term follow-up of neuropathy in patients with familial amyloid polyneuropathy after liver transplantation is still scarce. *Methods*: We describe the neuropathic features of 3 patients with the transthyretin Val30Met mutation. Each patient underwent liver transplantation at an early stage of neuropathy, as indicated by the absence of motor dysfunction and relative preservation of myelinated fibers in sural nerve biopsy specimens. *Results*: Although the patient with late-onset disease (at age 60 years) presented with the least amount of amyloid deposition, he had neuropathic progression after liver transplantation. An older early-onset (at age 40 years) patient reported a slight exacerbation of both somatic and autonomic neuropathic symptoms 10 years after transplantation. However, the younger early-onset (at age 28 years) patient did not exhibit characteristics suggestive of neuropathy 7 years after transplantation. *Conclusion*: Aging may determine the progression of neuropathy after liver transplantation.

Muscle Nerve **46:** 964–970, 2012

Abbreviations: CTR, cardiothoracic ratio; CVR-R, coefficient of variation of the R-R intervals; FAP, familial amyloid polyneuropathy; IVS, interventricular septum; TTR, transthyretin

Key words: amyloid; familial amyloid polyneuropathy; liver transplantation; neuropathy; transthyretin

Correspondence to: H. Koike; e-mail: koike-haruki@med.nagoya-u.ac.jp (or) G. Sobue; e-mail: sobueg@med.nagoya-u.ac.jp

Published online 18 June 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.23480

Familial amyloid polyneuropathy (FAP) is an hereditary amyloidosis that is typically caused by a mutation in transthyretin (*TTR*).[1–4] Initially, FAP