Published in final edited form as:
J Peripher Nerv Syst. 2012 June ; 17(2): 197–200. doi:10.1111/j.1529-8027.2012.00398.x.

CASE REPORT: Phenotypic presentation of the Ser63Del MPZ mutation

Lindsey J. Miller[1], **Agnes Patzko**[1], **Richard A. Lewis**[1], and **Michael E. Shy**[1,2]

[1]Department of Neurology, Wayne State University School of Medicine, Detroit, MI, USA

[2]Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI, USA

Abstract

Mutations in MPZ cause CMT1B, the second most frequent cause of CMT1. Elegant studies with Ser63del mice suggest that Ser63del MPZ is retained in the ER where it activates the unfolded protein response (UPR) that contributes to the neuropathy. Clinical information about patients with this mutation is limited. We present clinical and electrophysiological data on a large multigenerational family with CMT1B caused by Ser63del MPZ. The patients have a classical CMT1 phenotype that is much less severe than that of patients with Arg98Cys MPZ that also activates the UPR. These results suggest that clinical presentation along cannot predict which MPZ mutations will be retained in the ER and activate the UPR.

Introduction

Mutations in the gene Myelin Protein Zero (MPZ) cause Charcot-Marie-Tooth type 1B (CMT1B) (Hayasaka et al., 1993a), the second most frequent cause of autosomal dominant CMT1 (Nelis et al., 1996; Saporta et al., 2011). How *MPZ* mutations cause CMT1B is unknown but recent studies with Ser63del MPZ mice suggest that this particular mutation causes endoplasmic reticulum (ER) retention of the mutant protein with resultant activation of a canonical unfolded protein response (UPR) (Pennuto et al., 2008). Since the mice improve after genetically manipulating the UPR (Pennuto et al., 2008), these results suggest that medical manipulation of the UPR may be a rational therapeutic approach for patients bearing this and related mutations. Ser63del MPZ is known to cause CMT1B in humans (Hayasaka et al., 1993b). However, there is little detailed information about the phenotype of these patients with the exception of brief statements that patients appear similar to those with CMT1A (Defesche et al., 1990; Kulkens et al., 1993; Gabreels-Festen et al., 1996). A more detailed presentation of the Ser63del phenotype would be useful for several reasons. First, clinical trials involving patients depend on accurate knowledge of the phenotype and its natural history. Second, phenotypes of patients with CMT1B cannot easily be predicted based on other *MPZ* mutations. Most patients with CMT1B present with one of two extreme phenotypes: one with an infantile onset of symptoms including delayed walking and nerve conduction velocities (NCV) <10 m/s and a second with an adult onset and NCV often >40 m/s (Shy et al., 2004). Patients with “classic” CMT1 phenotypes that resemble CMT1A in which patients walk before a year of age, slowly develop symptoms within the first two decades of life and have NCV between 20 and 30 m/s are unusual for CMT1B (Shy et al., 2004). Thirdly, the severity of the phenotype has implications for future therapy. We have recently identified another MPZ mutation, R98C, that causes CMT1B(Warner et al., 1996;

Corresponding Author: Michael E. Shy, Department of Neurology, Carver College of Medicine, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242, USA. Tel: +319-353-5097, Fax: +319-384-7199, michael-shy@uiowa.edu.

Bai et al., 2006), ER retention of the mutant protein and UPR activation (Saporta et al., in press). Patients with R98C CMT1B have a severe early-onset neuropathy with NCV <10 m/s and do not walk independently until approximately 3 years of age (Shy et al., 2004; Bai et al., 2006). If Ser63del MPZ also causes a severe early-onset neuropathy, this would suggest that ER retention and UPR activation may uniformly cause severe neuropathies that may prove more difficult to treat.

We have identified and present a large multigenerational family with CMT1B caused by Ser63del. Several affected patients also had a mutation of Thr118Met in PMP22, known to cause a partial loss of function phenotype resembling mild HNPP (Shy et al., 2006). Patients were evaluated clinically and by electrophysiology.

Results

The pedigree of our kindred is provided in Fig. 1. Ten patients were evaluated at our clinic and their results are summarized in Table 1. Patients' ages ranged from 6 to 73 years. Only one patient reported a delay in walking, although two others did not know when they first walked independently. Motor nerve conduction velocities (MNCV) were between 12 and 30 m/s, in the range of what we typically find in patients with CMT1A (Saporta et al., 2011). The CMT neuropathy scores (CMTNS) were in the mild to moderate range for all patients (Shy et al., 2005). Interestingly, sensory abnormalities were more prominent than motor abnormalities (Table 1). Taken together, the data suggest that Ser63del caused a classical CMT phenotype with a normal onset of ambulation and mild progression of symptoms and signs within the first two decades of life (Harding and Thomas, 1980). These patients were far less severely affected than patients with R98C MPZ mutations who have been non-ambulatory before 21 years of age.

Discussion

Therapeutic approaches that will alleviate ER retention of misfolded proteins and decrease UPR activation are increasingly being considered in CMT. For example, sarcoplasmic/endoplasmic reticulum calcium pump (SERCA) inhibitors can potentially reduce ER stress by inhibiting calcium binding to disrupt calnexin function (Egan et al., 2002). SERCA inhibitors are therefore candidate therapies to treat certain forms of CMT. Since much of what is known about UPR activation in CMT1B comes from studies on Ser63del mice (Pennuto et al., 2008), we believe that it was important to thoroughly characterize the human phenotype with this mutation to make correlations between the mouse model and human patients more feasible. This is particularly true if human clinical trials may result from these studies.

These results show that Ser63del MPZ causes a classical CMT phenotype and demonstrate that phenotype alone cannot predict which patients will be candidates for treatments designed to reduce ER stress. For example Arg98Cys MPZ also is retained in the ER and activates the UPR. Yet it causes a clinically much more severe neuropathy in which patients don't begin to walk until they are 2–3 years of age and often require wheel chairs to ambulate by adulthood. These more severely impaired patients, with pronounced dysmyelination and axonal loss, may prove more difficult to treat than mildly affected patients where demyelination may be the primary abnormality. Future studies will need to be designed to determine which patients with CMT1B will be candidates for treatment trials designed to reduce ER stress and UPR activation.

Acknowledgments

The authors thank the patients for their efforts and participation. IRB approval has been obtained at Wayne State University for this study. The work was supported by grants from the NINDS (R01 NS41319A to M. E. S.), NINDS/ORD (U54NS065712-01 to M. E. S.) and from the Muscular Dystrophy Association and Charcot-Marie-Tooth Association (CMTA) (M. E. S.).

References

Bai Y, Ianokova E, Pu Q, Ghandour K, Levinson R, Martin JJ, Ceuterick-de Groote C, Mazanec R, Seeman P, Shy ME, Li J. Effect of an R69C mutation in the myelin protein zero gene on myelination and ion channel subtypes. Arch Neurol. 2006; 63:1787–1794. [PubMed: 17172621]

Defesche JC, Hoogendijk JE, de Visser M, de Visser O, Bolhuis PA. Genetic linkage of hereditary motor and sensory neuropathy type I (Charcot-Marie-Tooth disease) to markers of chromosomes 1 and 17. Neurology. 1990; 40:1450–1453. [PubMed: 2392234]

Egan ME, Glockner-Pagel J, Ambrose C, Cahill PA, Pappoe L, Balamuth N, Cho E, Canny S, Wagner CA, Geibel J, Caplan MJ. Calcium-pump inhibitors induce functional surface expression of Delta F508-CFTR protein in cystic fibrosis epithelial cells. Nat Med. 2002; 8:485–492. [PubMed: 11984593]

Gabreels-Festen AA, Hoogendijk JE, Meijerink PH, Gabreels FJ, Bolhuis PA, van Beersum S, Kulkens T, Nelis E, Jennekens FG, de Visser M, van Engelen BG, Van Broeckhoven C, Mariman EC. Two divergent types of nerve pathology in patients with different P0 mutations in Charcot-Marie-Tooth disease. Neurology. 1996; 47:761–765. [PubMed: 8797476]

Harding AE, Thomas PK. The clinical features of hereditary motor and sensory neuropathy types I and II. Brain. 1980; 103:259–280. [PubMed: 7397478]

Hayasaka K, Himoro M, Sato W, Takada G, Uyemura K, Shimizu N, Bird TD, Conneally PM, Chance PF. Charcot-Marie-Tooth neuropathy type 1B is associated with mutations of the myelin P0 gene. Nat Genet. 1993a; 5:31–34. [PubMed: 7693129]

Hayasaka K, Takada G, Ionasescu VV. Mutation of the myelin P0 gene in Charcot-Marie-Tooth neuropathy type 1B. Hum Mol Genet. 1993b; 2:1369–1372. [PubMed: 7694726]

Kulkens T, Bolhuis PA, Wolterman RA, Kemp S, te Nijenhuis S, Valentijn LJ, Hensels GW, Jennekens FG, de Visser M, Hoogendijk JE, Baas F. Deletion of the serine 34 codon from the major peripheral myelin protein P0 gene in Charcot-Marie-Tooth disease type 1B. Nat Genet. 1993; 5:35–39. [PubMed: 7693130]

Nelis E, Van Broeckhoven C, De Jonghe P, Lofgren A, Vandenberghe A, Latour P, LeGuern E, Mostacciuolo MS, Schlavon R, Palau F, Bort S, Upadhyaya M, Rocchi M, Archidiacono N, Mandich P, Bellone E, Silander K, Savontaus ML, Navon R, Goldberg-Stern J, Estivill X, Volpini V, Friedl W, Zerres K, Tyson J, Malcolm S, Holmberg B, Golmgren G, Mariman M, Gabreels-Festen AAWM, Yapijakis C, Vassilopoulos D, Clark C, Haites N, Hillbert P, Van Mahdergem L, Rautenstrauss V, Grehl H, Mountford R, Mann K, Bettecken T, Burgunder JM, Hanemann CO, Muller HW, Hertz JM, Schorderet DF, Kuntzer T, Wolf C, Kunert E, Muntoni F, Emmerick-Bock P, Orth U, Gal A. Estimation of the mutation frequencies in Charcot-Marie-Tooth disease type 1 and hereditary neuropathy with liability to pressure palsies: a European collaborative study. Eur J Hum Genet. 1996; 4:25–33. [PubMed: 8800924]

Pennuto M, Tinelli E, Malaguti M, Del Carro U, D'Antonio M, Ron D, Quattrini A, Feltri ML, Wrabetz L. Ablation of the UPR-mediator CHOP restores motor function and reduces demyelination in Charcot-Marie-Tooth 1B Mice. Neuron. 2008; 57:393–405. [PubMed: 18255032]

Saporta MA, Shy BR, Patzko A, Bai Y, Pennuto M, Ferri C, Kirschner D, Avila AM, Southwood C, Wu X, Gow A, Feltri ML, Wrabetz L, Shy ME. R98C Mpz arrests Schwann Cell development in mouse model of early onset Charcot Marie Tooth 1B. Brain. (in press).

Saporta AS, Sottile SL, Miller LJ, Feely SM, Siskind CE, Shy ME. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol. 2011; 69:22–33. [PubMed: 21280073]

Shy ME, Jani A, Krajewski KM, Grandis M, Lewis RA, Li J, Shy RR, Balsamo J, Lilien J, Garbern JY, Kamholz J. Phenotypic clustering in MPZ mutations. Brain. 2004; 127:371–384. [PubMed: 14711881]

Shy ME, Blake J, Krajewski K, Fuerst DR, Laura M, Hahn AF, Li J, Lewis RA, Reilly M. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology. 2005; 64:1209–1214. [PubMed: 15824348]

Shy ME, Scavina MT, Clark A, Krajewski KM, Li J, Kamholz J, Kolodny E, Szigeti K, Fischer RA, Saifi GM, Scherer SS, Lupski JR. T118M PMP22 mutation causes partial loss of function and HNPP-like neuropathy. Ann Neurol. 2006; 59:358–364. [PubMed: 16437560]

Warner LE, Hilz MJ, Appel SH, Killian JM, Kolodry EH, Karpati G, Carpenter S, Watters GV, Wheeler C, Witt D, Bodell A, Nelis E, Van Boreckhoven C, Lupski JR. Clinical phenotypes of different MPZ (P0) mutations may include Charcot-Marie-Tooth type 1B, Dejerine-Sottas, and congenital hypomyelination. Neuron. 1996; 17:451–460. [PubMed: 8816708]

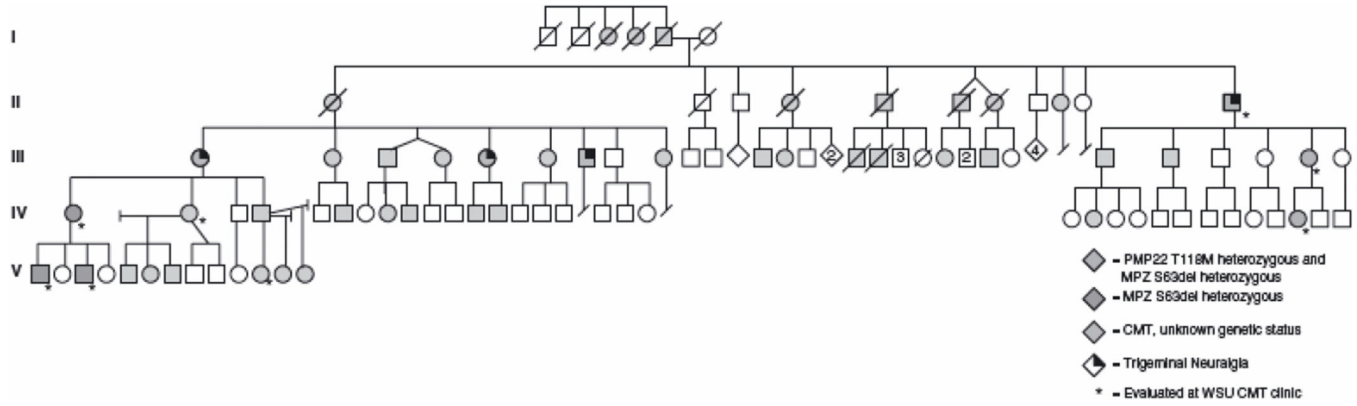

Figure 1.
The pedigree of our kindred.

Table 1

Evaluation results.

Individual	Onset	Delayed walking	Age at exam (years)	Median		Ulnar		Ambulation aids	Foot dorsi-flexion left/right	Vibration*	CMTNS	
				MNCV (m/s)	Distal latency	MNCV (m/s)	Distal latency				Total	Sensory
V-1	<2 years	−	18	20.4	3.93	33.3	4.87	FOs	5/5	Decreased to knees	9	6
V-3	<2 years	−	9	n/a	n/a	43.1	3.07	FOs	5/5	Decreased to knees	5	5
V-11	Early Childhood	+	8	28.3	3.93	30.7	3.53	FOs	5/5	Decreased at toes	7	5
IV-1	Childhood	−	41	15.9	4.5	27.9	4.00	FOs	5/5	Decreased to knees	11	8
IV-2	Childhood	−	42	12.1	6.63	22.4	3.60	FOs	5/5	Absent to knees	10	8
IV-21	<2 years	−	12	n/a	n/a	25.3	3.77	None	5/5	Decreased to knees	12	9
IV-30	<2 years	−	6	24.6	3.93	n/a	n/a	SMOs	5/5	Decreased to knee	9	5
III-26	n/a	n/a	47	31.7	7.73	27.9	4.57	None	n/a	n/a	n/a	n/a
III-30	Childhood	−	37	12.2	22.25	16.0	17.00	AFOs for balance	5/5	Decreased to knees	13	10
II-11	Childhood	n/a	73	17.7	5.33	20.5	4.83	Wheelchair	3/4	Absent to knees	19	10

*Decreased vibration equals a 5-s difference between the examiner and the patient at the same site using a 128 Hz tuning fork.