CASE REPORT

Peripheral nerve involvement in classic homocystinuria: an unusual association

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SUMMARY

Classic homocystinuria is one of the most common causes of hereditary hyperhomocysteinemia. It is an autosomal recessive and multisystemic disorder due to cystathionine β -synthase deficiency. We described a case of an 18-year-old Portuguese man with an ischaemic stroke, who was subsequently diagnosed with classic homocystinuria [Thr191Met (c.572C>T) CBS mutation] associated with a sensorimotor neuropathy. The patient had a good clinical and metabolic response to pyridoxine plus methionine-restricted diet after 12 months of treatment. Neurophysiological re-evaluation with nerve conduction studies disclosed an improvement on the peripheral nerve lesion. Central nervous system manifestations in classic homocystinuria have been well documented, but this is to the best of our knowledge the first report of an association with peripheral neuropathy, which improved after hyperhomocysteinemia treatment.

BACKGROUND

Inherited homocystinurias are a wide group of homocysteine metabolic disorders related to defects of the transsulfuration and remethylation pathways, leading to moderate-to-severe hyperhomocysteinemia.^{1–2} Cystathionine β -synthase (CBS) deficiency causes classic homocystinuria (CH), an autosomal recessive multisystem disorder with a greatly variable phenotypic expression including central nervous system involvement,^{1–6} but no association with peripheral nerve disorder has been previously documented.

CASE PRESENTATION

An 18-year-old Portuguese man was admitted in the stroke unit with a right hemispheric ischaemic infarct. He is the first son of Portuguese consanguineous parents with developmental delay, dorsal scoliosis and bilateral myopia since infancy. There were no known familial disorders. There was history of no drug or toxic exposure (including alcohol). At the emergency room, in addition to left hemiparesis related to acute stroke, there was loss of position and vibration sense in both hallux and decreased deep tendon reflexes in the lower limbs, except for the triceps surae that were abolished. Pinprick sensation was normal. There were no high arched feet, hammertoes or shortened Achilles tendons. Neurophthalmological examination disclosed bilateral myopia without ectopia lentis. A general physical examination revealed marfanoid habitus with dolichostenomelia and dorsal scoliosis. No cardiac, lung, skin involvement or joint

hypermobility were identified. His parent's clinical and neurophysiological examinations were normal.

INVESTIGATIONS

Brain MRI showed an acute ischaemic infarct of the right middle cerebral artery. A normal transthoracic echocardiography was disclosed, namely without criteria for aortic root dilation. Biochemical studies revealed serum total homocysteine of 353.3 μ M (normal <14.0), serum methionine of 880.0 μ M (normal <40.9) and urinary homocysteine of 403.3 μ mol/mmol creatinine (normal <4.0). The patient's clinical features and metabolic profile were suggestive of CH, confirmed by molecular study with identification of Thr191Met (c.572C>T) CBS mutation in homozygosity by DNA gene sequencing.

Motor and sensory nerve conduction studies (NCS) showed a mild axonal sensorimotor neuropathy (figure 1A and table 1A). No conduction block or abnormal temporal dispersion was found. Needle electromyography revealed no denervation potentials.

Haemogram, erythrocyte sedimentation rate, C reactive protein, glucose, haemoglobin A1c, renal function, thyroid profile, vitamins (B₆, B₉ and B₁₂), serum methylmalonic acid, serum protein electrophoresis and autoimmunity (antinuclear, antidouble-stranded DNA, extractable nuclear antigens and antineutrophil cytoplasmic autoantibodies) disclosed no abnormalities. Serology for HIV 1/2 and hepatitis B/C virus was also negative.

TREATMENT

Treatment with pyridoxine (titrated up to 900 mg daily) plus methionine-restricted diet was started as well acetylsalicylic acid for vascular secondary prevention.

OUTCOME AND FOLLOW-UP

The metabolic profile had clearly improved after 12 months of pyridoxine plus methionine-restricted diet (serum total homocysteine of 70.0 μ M and serum methionine of 60.0 μ M). There was a partial recovery of left hemiparesis. Sensory disturbances in both halluxes improved, but hyporeflexia persisted in the lower limbs and the triceps surae remained abolished. The neurophysiological evaluation with NCS after treatment disclosed an improvement on the peripheral nerve lesion (figure 1B and table 1B).

DISCUSSION

CH is the most prevalent type of inherited homocystinuria.^{1–3–5} More than 160 mutations in the

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Figure 1 Waveforms recorded in motor and sensory nerve conduction studies of the lower limbs before (A1–4) and 12 months after (B1–4) treatment.

CBS gene (chromosome 21q22.3) have been reported.³ Classically, there are two kinds of phenotypes related to pyridoxine responsiveness, being the non-responsive form generally more severe than the responsive one.¹ In contrast to the majority of European countries, Thr191Met *CBS* mutation (pyridoxine-non-responsive phenotype) is the most prevalent in Portugal, Spain and American Hispanics.³

The cardinal biochemical features of the disease are markedly increased levels of serum total homocysteine (usually above 50 µM) and serum methionine plus increased urinary excretion of homocysteine.^{1–3 5 6}

The phenotypic expression is quite heterogeneous and may include developmental delay, seizures, ectopia lentis, severe myopia, marfanoid habitus with dolichostenomelia, skeletal abnormalities and thromboembolic events.^{1–6} Despite the well-known central nervous system complications with mental retardation, seizures and cerebrovascular disease, involvement of the peripheral nerves has never been reported (a systematic review was carried out in the PubMed using the following keywords: homocystinuria and neuropathy, *CBS* deficiency and neuropathy, hyperhomocysteinemia and neuropathy).

The neuropathy-related signs were both subtle, which is usually the case in the metabolic disorders spectrum. NCS disclosed a slight decrease in motor and sensory nerve amplitudes with minor increase of distal motor latencies and prolonged F-waves, with no conduction block or abnormal temporal dispersion. A mild decrease on motor and sensory nerve conduction velocities was found, according to an axonal sensorimotor neuropathy with a secondary demyelinating process. Criteria for an inflammatory demyelinating neuropathy were not fulfilled.⁷

In CH, the general therapeutic approach is to lower or even normalise serum total homocysteine levels.^{1 2 4–6} There are different options available, which include pyridoxine, folate and vitamin B₁₂ supplements, methionine-restricted diet and betaine.^{1 2 4 6} Although our patient has a pyridoxine-non-responsive phenotype

Table 1 Motor and sensory nerve conduction studies before (A) and 12 months after (B) treatment†

	CMAP				SNAP		
	DML (ms)	Amp (mV)	MCV (m/s)	F-wave min/max	DL (ms)	Amp (µV)	SCV (m/s)
<i>Ulnar</i>	(n<3.4)*	(n>7.0)	(n>49.0)		(n<3.1)	(n>15.0)	(n>45.0)
A	2.8	12.0	44.6	39.2/44.1	2.5	52.0	52.0
B	2.9	11.8	47.1	39.0/43.1	2.6	37.0	51.9
<i>Peroneal</i>	(n<5.8)	(n>3.3)	(n>40.0)		(n<2.3)	(n>4.1)	(n>40.0)
A	5.8	3.0	36.7		4.0	1.5	32.5
B	4.3	4.9	39.2		2.1	4.6	40.5
<i>Tibialis posterior</i>	(n<6.1)	(n>3.9)	(n>40.0)				
A	6.7	6.6	39.2	75.2/82.0			
B	4.4	5.1	39.1	67.0/69.3			
<i>Suralis</i>					(n<2.5)	(n>6.0)	(n>40.0)
A					3.5	8.4	35.7
B					2.0	12.0	45.0

Italic text represents changed values according to normal values listed in parenthesis.

*Normal values are listed in parentheses.

†Temperature was adequately controlled for in the two neurophysiological studies (30°C).

CMAP, compound muscle action potential; SNAP, sensory nerve action potential; DML, distal motor latency; Amp, amplitude; MCV, motor conduction velocity; DL, distal latency; SCV, sensory conduction velocity.

(Thr191Met *CBS* mutation), he had a good metabolic response to pyridoxine plus methionine-restricted diet after 12 months of treatment. Concomitantly, NCS revaluation showed an improvement on the peripheral nerves dysfunction, which we may interpret as a positive response to treatment. It is worthy to note that the lack of pyridoxine responsiveness in this kind of phenotypes is not always total, as some patients may indeed respond at least partially. So pyridoxine should also be included in treatment of such patients.² Adjuvant methionine-restricted diet has helped lowering serum total homocysteine levels by enhancing the remethylation pathway of homocysteine metabolism.

In contrast to CH, homocysteine remethylation pathway defects have been associated with peripheral neuropathy.^{8–11} Several theories have been postulated to clarify the pathophysiological mechanisms. One suggests that the central core of neuronal impairment is the decreased availability of methionine and its metabolite S-adenosylmethionine due to impairment of homocysteine remethylation.^{8–10} The S-adenosylmethionine is a methyl donor crucial for methylation of myelin sheath compounds (myelin basic protein and lipids), which is essential to stabilise its architecture.^{8–9} If this physiological system fails, the myelin sheath becomes abnormal, leading to neuronal demyelination.^{8–9} Other proposals are that hyperhomocysteinemia may induce vascular endothelial lesion, and direct neuronal damage through free radicals and cytosolic calcium accumulation, mitochondrial dysfunctions, apoptotic pathways triggering and excitotoxic amino acid-mediated injury.^{9–10–12}

Our case, being a defect of transsulfuration pathway, the biosynthesis of methionine is not compromised. Still, it shares with the other inherited homocystinurias the markedly high serum total homocysteine levels and its cellular consequences. On the other hand, the final product of this homocysteine metabolic

pathway is cysteine, which is required for the biosynthesis of a powerful physiological antioxidant called glutathione.² Perhaps, the chronic exposure of the peripheral nerves to severe hyperhomocysteinemia and the disequilibrium of the antioxidant system may have induced neuronal injury over time with subsequent peripheral neuropathy development.

It remains unclear why peripheral nervous system involvement in CH had not been described yet, but we postulate that the indolent course of the peripheral neuropathy and its subtle signs may be responsible by its underdiagnosis.

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REFERENCES

- Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 2: homocystinuria, organic acidurias, and urea cycle disorders. *Arch Neurol* 2010;67:148–53.
- Schiff M, Blom HJ. Treatment of inherited homocystinurias. *Neuropediatrics* 2012;43:295–304.
- Alcaide P, Krijt J, Ruiz-Sala P, et al. Enzymatic diagnosis of homocystinuria by determination of cystathionine-ss-synthase activity in plasma using lc-ms/ms. *Clin Chim Acta* 2015;438:261–5.
- Debette S, Germain DP. Neurologic manifestations of inherited disorders of connective tissue. *Handb Clin Neurol* 2014;119:565–76.
- Goda SK, Abu Aqel YW, Al-Aswad MR, et al. Production of synthetic methionine-free and synthetic methionine-limited alpha casein: protein foodstuff for patients with homocystinuria due to cystathionine beta-synthase deficiency. *Protein J* 2010;29:44–9.
- Kalidas K, Behrouz R. Inherited metabolic disorders and cerebral infarction. *Expert Rev Neurother* 2008;8:1731–41.
- Van den Bergh PY, Hadden RD, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. *Eur J Neurol* 2010;17:356–63.
- Tsuji M, Takagi A, Sameshima K, et al. 5,10-methylenetetrahydrofolate reductase deficiency with progressive polyneuropathy in an infant. *Brain Dev* 2011;33:521–4.
- Fratini D, Fusco C, Uchino V, et al. Early onset methylmalonic aciduria and homocystinuria cblc type with demyelinating neuropathy. *Pediatr Neurol* 2010;43:135–8.
- Chaabene-Masmoudi A, Mesrati F, Zittoun J, et al. Insidious peripheral neuropathy occurring under treatment in infantile MTHFR deficiency. *J Inher Metab Dis* 2009;32(Suppl 1):S303–306.
- Nishimura M, Yoshino K, Tomita Y, et al. Central and peripheral nervous system pathology of homocystinuria due to 5,10-methylenetetrahydrofolate reductase deficiency. *Pediatr Neurol* 1985;1:375–8.
- Mattson MP, Shea TB. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. *Trends Neurosci* 2003;26:137–46.

Learning points

- ▶ Classic homocystinuria phenotypic expression is greatly variable.
- ▶ Central nervous system complications, including development delay, seizures and cerebrovascular disease, are well-recognised features.
- ▶ To the best of our knowledge this is the first report of peripheral nerve involvement in classic homocystinuria.
- ▶ Peripheral neuropathy improvement has occurred after hyperhomocysteinemia treatment with pyridoxine and methionine-restricted diet.

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