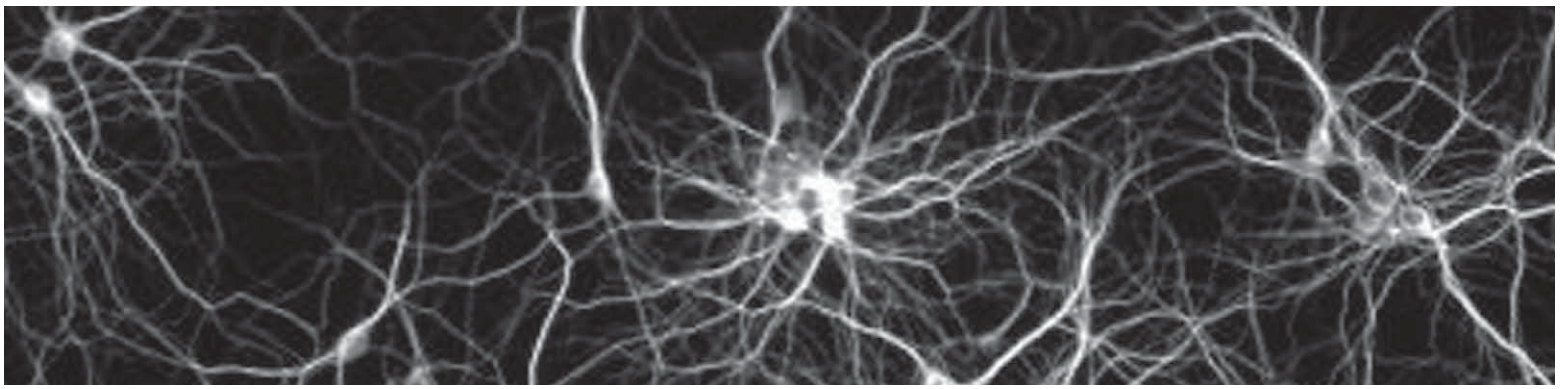

Chronic inflammatory demyelinating polyneuropathy superimposed on hereditary neuropathy with liability to pressure palsy

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ABSTRACT – *Objective:* Herein we present a case of deterioration of hereditary neuropathy with liability to pressure palsy (HNPP), which presented with clinical and electrophysiological signs of chronic inflammatory demyelinating polyneuropathy (CIDP). *Case report:* A 31-year-old man with a former diagnosis of HNPP developed slowly progressive motor and sensory deficit five months after influenza vaccination. Clinically, it presented as distal symmetric muscle weakness of both legs, areflexia, and ataxic and peroneal gait. Nerve conduction studies revealed signs of demyelination and conduction blocks (CB) in motor fibers of upper and lower limbs. Sensory nerve action potentials (SNAP) were normal and no CB in sensory fibers was detected. *Results:* The diagnosis of CIDP was established according to the European Federation of Neurological Societies (EFNS) guidelines. The patient was submitted to prolonged prednisone treatment (60 mg *per* day) and impressive improvement of clinical and neurographic parameters occurred after 9 months. We assumed that HNPP in our patient was associated with superimposed immune mediated affection of the same target tissue. *Conclusion:* Peripheral nerves in patients suffering from hereditary polyneuropathies may be highly susceptible to secondary immune damage due to antigenic variation or alteration in the blood-nerve barrier. Unusual and sudden deterioration of chronic hereditary neuropathy may be explained

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by sudden, immune mediated inflammation, i.e. by superimposed autoimmune polyneuropathy. In order to prevent future damage to the peripheral nervous system, immunosuppressive or immunomodulatory treatment should be considered in these patients.

Key words: autoimmunity, chronic inflammatory demyelinating polyneuropathy, hereditary neuropathy with liability to pressure palsy

INTRODUCTION

Hereditary neuropathy with liability to pressure palsy (HNPP) is a disease with autosomal dominant inheritance. The prevalence is estimated to 2-5 *per* 100 000 people, and both sexes are equally affected. HNPP is associated with mutation or deletion of PMP22 gene on chromosome 17p11.2. There is no specific therapy. Intensive physiotherapy should be applied immediately after the onset of nerve palsy. Preventive measures include avoiding compression of peripheral nerves by abnormal positions and movements. The condition can sometimes be revealed later in life when individuals develop an acquired unrelated neuropathy due to autoimmunity (1).

Chronic inflammatory demyelinating polyneuropathy (CIDP) is common acquired autoimmune neuropathy with variable presentation and clinical course. At present, most acquired demyelinating neuropathies of otherwise unknown etiology are considered to be a form of CIDP (2). The prevalence of 1 to 7.7 *per* 100,000 is reported (3). The symptoms of motor and sensory deficits develop insidiously with progressive or relapsing phase of over 8 weeks. An acute onset resembling Guillain-Barré syndrome can develop in the minority of patients. Acute-onset CIDP in a patient initially diagnosed as Guillain-Barré syndrome is likely if deterioration continues for more than two months of the onset (4). The clinical and electrodiagnostic criteria proposed by the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) have been successfully used in clinical trials, and according to Rajabally *et al.*, these criteria have 81% sensitivity and 90% specificity (5,6). Based on the EFNS/PNS clinical criteria, typical CIDP should be considered in any patient with progressive, stepwise, or recurrent symmetric proximal and distal weakness, generalized areflexia without wasting, and sensory dysfunction with preferential loss of vibration or joint position sense developing over at least two months. Electrodiagnostic tests for primary demyelination are mandatory and include prolongation of motor distal latencies, reduction of motor conduction velocities, prolongation of F-wave latencies, absence of F-waves, partial motor conduction blocks, abnormal temporal dispersion, and increased duration of distal compound muscle action potentials.

Hereditary neuromuscular disorders may be associated with immune response against primary affected target tissue antigens (7,8). The first report of prednisone responsive hereditary neuropathy drew attention to the possibility of association of hereditary and acquired autoimmune peripheral neuropathy (9). The subgroup with stepwise progression of Charcot-Marie-Tooth disease (CMT) may include patients in whom an autoimmune response against released hidden myelin antigens occurs. In these patients, myelin proteins and glycolipids could be recognized as altered self-antigens and induce production of autoantibodies (10). If deterioration of clinical presentation in a patient with CMT indicates possible autoimmune reaction, it is reasonable to consider immunosuppressive therapy which may prevent progression of polyneuropathy and severe disability.

In this case report, we present a patient with deterioration of HNPP after vaccination, with clinical and electrophysiological signs that met the CIDP diagnostic criteria.

CASE REPORT

A 31-year-old man complained of low back pain after physical exercise. On neurological examination, Lasegue sign was bilaterally positive and ankle reflexes were symmetrically reduced. The electroneurographic parameters indicated only mild prolongation of deep peroneal nerve motor latencies and mild reduction of sural nerves conduction velocities (NCV) (Table 1). Blood cell count, serum biochemistry (Fe, CK, HbA1c, UIBC, ferritin, Cu, B12), tests for viral and bacterial infections (HbsAg, HCV, HIV, *Borrelia burgdorferi*) and tumor antigens (CEA, Ca 19-9, AFP, PSA) showed no abnormality. Genetic analysis revealed PMP22 gene deletion and the diagnosis of HNPP was estab-

Table 1. *Electroneurographic parameters*

Nerve	Site	Parameter	Visit 1	Visit 2	Comment	Visit 3	Normal values (11)
Motor nerves							
Left median	Wrist	mDL	3.25	3.45		3.0	<3.8
		CMAP	4.6	2.1		6.3	>5.2
		CMAP d	9.7	16.9		10.2	<16.3
	Elbow-wrist	CV	52.7	6.0		51.1	>47
		CMAP	4.0	0.2	CB	6.0	>5.2
		CMAPd	8.8	24.8		11.9	<16.3
Left ulnar	Wrist	mDL	3.4	3.09		3.8	<3.7
		CMAP	8.2	4.9		4.3	>7.9
		CMAPd	8.2	19.9		15.6	<17.3
	Elbow-wrist	CV	52.3	7.4		48.1	>52
		CMAP	8.6	1.2	CB	4.2	>7.9
		CMAPd	7.8	24.3		16.9	<17.3
		F	17.8	31.5		14.3	<25
Left common peroneal	Ankle	mDL	9.1	11.9		8.15	<2.5
		CMAP	5.4	5.2		4.8	>5.1
		CMAPd	11.8	1.2	CB	13.8	<14.3
	Below head of fibula	CV	53.6	19.8		44.9	>40
		CMAP	5.4	5.2		3.9	>5.1
		CMAPd	12.5	19.9		12.7	<14.3
		F	40.3	59.8		43.6	<50
Sensory nerves							
Left median	Wrist-digit	SNAP	9.2	0.34		6.9	>19
		CV	63.5	32.1	CB?	48.3	>44
Left ulnar	Wrist-digit 2	SNAP	7.2	2.04		4.6	>20
		CV	63.2	40.0		47.4	>44
Left sural	Distal third of lower leg-ankle	SNAP	8.5	0	CB?	7.0	>1.9
		CV	48.1			47.2	>46
Motor nerves							
Right median	Wrist	mDL	3.35	2.9		4.55	<3.8
		CMAP	5.8	3.3		4.8	>5.2
		CMAP d	6.3	18.2		14.1	<16.3
	Elbow-wrist	CV	57.2	8.5		47.5	>47
		CMAP	5.9	0.2	CB	3.6	>5.2
		CMAPd	7.2	20.8		12.2	<16.3
Right ulnar	Wrist	mDL	3.09	2.75		3.35	<3.7
		CMAP	7.9	9.7		6.4	>7.9
		CMAPd	9.2	20.3		14.3	<17.3
	Elbow-wrist	CV	55.4	9.4		66.7	>52
		CMAP	7.7	2.0	CB	6.3	>7.9
		CMAPd	9.3	22.9		12.5	<17.3
		F	21	36.5		23.6	<25
Right common peroneal	Ankle	mDL	11.55	11.55		9.,11	<2.5
		CMAP	5.1	3.0		3.4	>5.1
		CMAPd	11.2	19.9		13.2	<14.3
	Below head of fibula	CV	48.0	20.7		44.6	>40
		CMAP	4.9	0.4	CB	3.9	>5.1
		CMAPd	10.8	23.8		14.8	<14.3
		F	42.5	62.5		45.2	<50
Sensory nerves							
Right median	Wrist-digit 2	SNAP	9.2	0	CB	6.2	>19
		CV	66.7			46.9	>44
Right ulnar	Wrist-digit 2	SNAP	9.8	1.0	CB	9.5	>20
		CV	65.3	32.1		44.9	>44
Right sural	Distal third of lower leg-ankle	SNAP	7.3	0	CB	8.2	>1.9
		CV	47.9			45.8	>46

SNAP = sensory action potential-orthodromic study (micro V); CMAP = compound muscle action potential (mV); mDL = motor distal latency; CV = conduction velocity (m/s); CMAPd = CMAP duration (ms); F = minimal F wave latency (ms); CB = conduction block; Visit 1 = hereditary neuropathy with liability to pressure palsy diagnosed; Visit 2 = chronic inflammatory demyelinating polyneuropathy diagnosed; Visit 3 = after CIDP treatment

lished. He was very well and without any sensory or motor alteration on neurological examinations in the following years.

Six years later, five months after influenza vaccination, he gradually started developing progressive motor and sensory deficit in lower limbs. Neurological examination revealed reduced deep tendon reflexes in upper limbs, hypotrophy and weakness of both tibial anterior muscles with foot drop, diminished deep tendon reflexes and reduced vibration sense in lower limbs. The gait was peroneal and slightly ataxic. Nerve conduction study disclosed multiple conduction blocks (CB) in motor fibers in four analyzed nerves of upper and lower extremities with prolonged F-wave latencies, prolonged and time-dispersed M potentials and decreased sensory nerve conduction velocity. CBs were observed at non-entrapment sites. Sensory nerve action potentials (SNAP) were normal and no CB in sensory fibers was detected (Table 1).

Blood cell count and serum biochemistry were normal. ELISA test for anti-ganglioside antibodies (GD1b) were highly positive. According to the EFNS guidelines, the CIDP diagnosis was established and immunosuppressive treatment was started with administration of prednisone at a daily dose of 60 mg (5). After 9 months of corticosteroid treatment, full recovery of clinical and electroneurographic parameters was achieved and slow tapering of prednisone for the next 10 months was performed.

DISCUSSION

A superimposed immune mediated neuropathy developed in the patient with HNPP. It occurred five months after influenza vaccination. The clinical and electrophysiological presentation of immune mediated neuropathy was recognized as a symmetric distal, predominantly motor form of CIDP. Slow progression of the disease over two months excluded the possibility of Guillian-Barré syndrome, whereas reduced vibration sense and full response to steroid treatment excluded multifocal motor neuropathy (12).

Many genetic neuromuscular disorders are caused by mutations or deletions of ubiquitously expressed genes that play critical roles in RNA metabolism, leading to their dysfunction (13-15). A change in these proteins may lead to the loss of immune self-tolerance. Inherited neuromuscular disorders may be associated with immune mediated superimposed affection of the same target tissue. If not recognized, this association presents as deterioration of the primary, inherited, disease (8). Early observations of inflammatory myopathy with facioscapular distribution were the basis for the hypothesis of polymyositis superimposed on facioscapular muscular dystrophy (8). The majority of patients with polymyositis/dermatomyositis (PM/DM) and other systemic autoimmune diseases produce organ-specific autoantibodies. Survival motor neuron 1 (SMN1) is well known as a causative gene for spinal muscular atrophy (SMA), whereas mutations of glycyl- and tyrosyl-tRNA synthetases are identified as a cause of distal SMA and CMT 1A. However, at the same time, SMN complex is an autoantigen recognized in patients with PM (16). In addition, mutations of the common autoantigens in PM/DM, aminoacyl tRNA synthetases, cause another genetic neuromuscular disorder, distal SMA, or CMT 1A (16).

The subgroup with stepwise progression of CMT may include patients in whom an autoimmune humoral response directed against myelin proteins occurs (7). There are several possible explanations for this scenario. It could be that these patients have additional immunosusceptibility to inflammatory demyelinating polyneuropathy. In case of CMT 1A, they have overexpressed PMP22, which already renders their peripheral nerves liable to demyelination and superimposed inflammatory demyelinating disorder, thus it may be more likely to occur in these individuals than in genetically normal subjects (7,10,16,17). Inherited polyneuropathy may expose myelin antigens or the gene duplication may contain genes that modify the immune response in some patients. In mice heterozygously deficient in the myelin protein zero gene, T cells show enhanced reactivity to myelin components and immune deficiency results in less severe peripheral nerve disease (18). Of course, it remains possible that these CMT patients with a stepwise disease progression simply have coincidental inflammatory neuropathy and CMT, but immunology research in this field suggests that, in this group of patients, immune mediated mechanisms relate the two conditions (7,8).

The term autoantigenesis is defined by Doyle and Mamula as the change that arises in self-proteins as they break self-tolerance and trigger autoimmune B and/or T cell response (19). Between 50% and 90% of proteins in the human body acquire post-translational modification. Those post-translational modifications can create new self-antigens by altering immune processing and presentation. This kind of modification can arise either by enzymatic

modification or can occur spontaneously. Many aspects of protein chemistry are then altered, including primary and tertiary structure, biological function and proteolytic degradation. Any of these can be a case of failure of self-tolerance. Certain cellular processes such as aging, disease, inflammation and trauma are known to increase the frequency of post-translational modifications (19,20). Among the most apparent post-translational protein modifications are the myriad of phosphorylation events that communicate signals originating at the cell surface through the cytoplasm and eventually to the nucleus (21). Other well-studied protein modifications include methylation and glycosylation, which are required for the biological function of various proteins. Classical biochemistry tells us that 20 amino acids make up most proteins in nature. Closer examination reveals a number that by far exceeds 20 original structures. Indeed, when post-translational modifications are considered, more than 140 unique amino acids compose proteins (19,22). A number of other modifications that arise in proteins after their synthesis might influence the central and peripheral mechanisms of tolerance of lymphoid cells, as well as the induction of autoimmune responses. The common post-translational modifications associated with autoimmune responses are described in multiple sclerosis, rheumatoid arthritis, celiac disease and atherosclerosis (20,23,24). One explanation for the lack of tolerance is that these post-translationally modified proteins are not present in the thymus during T cell development and the modifications may arise in the periphery due to different biochemical conditions (e.g., pH, inflammation, etc.). Moreover, upon initial stimulus by modified proteins, the response may then be amplified to other sites on the protein (intramolecular epitope spreading) (19).

Influenza vaccine triggered CIDP in our patient with primary HNPP, causing stepwise worsening of the clinical and EMG signs of polyneuropathy. It is possible that immune autoreactivity caused disease progression after post-translational change in myelin proteins or vaccination heightened subclinical immune response to these proteins. The same possibility is open for CMT patients with severe toxic polyneuropathies after vinca alkaloids (vincristine) administration. The breakdown of tubuline components may be the only underlying mechanism, but secondary damage *via* autoreactivity to post-translationally changed proteins is also possible. These processes result in neo self-antigens and they could be presented to T cells and immune system can lose tolerance. It is not clear when the tolerance to newly arising self-proteins is maintained and when it is not (19). To our knowledge, there are few reports of deterioration of CIDP after influenza vaccination and one case report of CIDP associated with HNPP (12).

CONCLUSION

It is clear that post-translational protein modifications can profoundly affect the recognition of autoantigens and self-tolerance of the immune system. Recent studies have suggested that there are times when the presence or absence of post-translational alterations in self-proteins can profoundly affect antigen recognition in immune functions. This is of special interest in the field of inherited neuromuscular diseases where congenital change in various proteins may lead to additional susceptibility to the immune response to the same target tissue. The pathways that control post-translational modifications may become targets of immunotherapeutic strategies to alter the states of autoimmunity *versus* immune tolerance (18).

The stepwise worsening in patients with inherited neuromuscular disorders may be a representation of additional underlying autoimmune process and immunosuppressive/immunomodulatory therapy may be a valuable treatment option to prevent future damage to the peripheral nervous system.

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Kronična upalna demijelinizirajuća polineuropatija superponirana na nasljednu neuropatiju sa sklonošću kompresivnoj kljenuti

SAŽETAK – *Cilj:* U članku prikazujemo bolesnika u kojeg je nastalo pogoršanje prethodno dijagnosticirane nasljedne motorne neuropatije sa sklonošću kompresivnim kljenutima (HNPP), koje je bilo uzrokovano superpozicijom stečene polineuropatije koja temeljem elektroneurografskih parametara i dinamike kliničke slike odgovara kroničnoj upalnoj demijelinizirajućoj polineuropatiji (CIDP). *Prikaz slučaja:* Muškarac u dobi od 31 godine s ranije postavljenom dijagnozom HNPP-a razvio je sporo napredujući motorni i senzorni deficit pet mjeseci nakon cijepljenja cjepivom protiv gripe. U kliničkoj slici bila je vidljiva simetrična mišićna slabost obje noge s nedostatkom refleksa, ataksijom i peronealnim hodom. Analiza parametara perifernih živaca uputila je na znakove demijelinizacije i blokova provođenja u motoričkim vlaknima živaca u gornjim i donjim udovima. Osjetni živčani akcijski potencijali bili su normalni, bez zabilježenih blokova provođenja u osjetnim vlaknima. *Rezultati:* Dijagnoza CIDP-a postavljena je na temelju smjernica Europskog udruženja neuroloških društava (EFNS). Bolesnik je podvrgnut dugotrajnoj terapiji prednizolonom (60 mg na dan), što je nakon 9 mjeseci dovelo do značajnog oporavka kliničkih i neurografskih pokazatelja. Pretpostavili smo da je pogoršanje kliničke slike HNPP-a u našeg bolesnika bilo barem dijelom povezano sa superponiranim, imuno posredovanim oštećenjem istog ciljnog tkiva. *Zaključak:* Moguće je da su periferni živci u bolesnika s nasljednim polineuropatijama, zbog antigenski izmijenjene strukture ili poremećaja barijere periferni živac-krv, naročito osjetljivi na sekundarna imuno oštećenja. Neočekivano i iznenadno pogoršanje kronične nasljedne neuropatije može se objasniti iznenadnom, imuno potaknutom upalom, odnosno superpozicijom autoimune polineuropatije. Kako bi se spriječila nova oštećenja perifernog živčanog sustava u tih bolesnika treba razmotriti primjenu imunosupresivnog ili imunomodulacijskog liječenja.

Ključne riječi: autoimunost, CIDP, HNPP