DIAGNOSTIC CONSIDERATIONS IN A CASE OF MULTIPLEX MONONEUROPATHY

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CASE STUDY

We report the case of a 59-year-old woman who was referred to our Neurology Department from a hematological clinic, where she was recently diagnosed with hemochromatosis.

Her medical problems were apparent in april 2008, when she was hospitalized for an acute coronarian syndrome (unstable angina but no myocardial infarction); echocardiography revealed left ventricle hypertrophy with delayed relaxation diastolic dysfunction and a minimal pericardial effusion (3 mm width). Her blood pressure values were mildly elevated. Concomitantly she was diagnosed with a chronic hepato-pancreatitis, with abnormal high values of seric ALT (166 UI/mL), AST (103 UI/mL), GGT (344 UI/mL), alkaline phosphatasis (154 UI/mL), amylasis (191 UI/mL) and total bilirubin (1.52 mg/dL). Seric protein electrophoresis was within normal range of values. Testing for viral hepatitis type B and C was negative. Abdominal echography showed moderate hepato-splenic enlargement with hyperechogenicity suggestive for fibrosis and no evident biliary pathology. Pancreas had normal size and moderate hyperechogenicity, too. Her fasting blood glucose was elevated (134 mg/dL); her oral glucose tolerance test revealed diabetes mellitus which responded well to dietary measures. Her blood cell count was within normal range; she had no renal impairment or urinary infection. She had a mild dyslipidemia with both hypercholesterolemia (total-cholesterol 228 mg/dL, LDL-cholesterol 61 mg/dL) and mild hypertrigliceridemia (159 mg/dL). Her ESR and fibrinogenemia were normal, but she had a high reactive C protein (++); she had no fever and no signs of systemic inflammation. The episode resolved under treatment and rest; in august 2008 her biochemical abnormalities were remitted. A high index of suspicion from an internal medicine specialist lead to a hemochromatosis screening, which revealed high values of seric ferritin (656.2 ng/mL, normal values = 16-186 ng/mL in postmenopausal women) and normal sideremia and transferrin saturation. She was than referred to a hematological department, where these laboratory values were confirmed. She had no history of repeated transfusions or anemia, so a hereditary hemochromatosis was suspicionned. Her HLA-A3 typing was negative. There was no

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possibility for genetic testing. The family history was irrelevant because of scarce reliable data. The patient had a 35-year-old son, apparently in good health.

In August 2008 the patient developed acutely (in a matter of a few days) asymmetric paresthesia with numbness and tingling in the lower limbs (much more marked on the left side) and than in hands (right hand more than left). She also noticed unsteady gait with impaired equilibrium. After a few days, her neurological symptoms reached a plateau intensity that kept constant for the next 6 weeks, until she was examined in our department. At presentation, her symptoms were mostly sensitive, with paresthesia and numbness asymmetrically in hands and feets (more marked on the left foot and right hand). She had tactile hypoesthesia in the territory of the left median, right ulnar and left peroneus nerves and a diminution of positional and vibratory sense more marked in the lower limbs, with an unsteady gait and an abnormal Romberg sign, suggestive of neuropathic ataxia. Her deep tendinous reflexes were diminished in the symptomatic territories. She had no cranial nerves involvement, no pyramidal signs and no evident autonomic dysfunction. She had no fever and no evident signs of systemic disease; for the last few years she complained of arthralgies of the small metacarpofalangial and interfalangial joints in both hands and also of hips and knees. She also noticed whitening of her hands after cold exposure.

The nerve conduction studies confirmed the mononeuropathy multiplex pattern of involvement of both motor and sensitive nerves, showing asymmetric reduction of motor and sensitive amplitudes in the left median and right ulnar nerves and slightly prolonged distal latencies and also lower motor amplitudes in the left tibialis and lower sensitive conduction velocities in the left peroneus nerve.

We diagnosed an acute onset, subacute evolution mononeuropathy multiplex of axonal type with large and smaller fibers involvement.

An extensive differential diagnostic work-up was initiated.

Fasting blood glucose was 106 mg/dL; Hb A1c revealed a fair glycemic control. Inflammation markers were normal (ESR, plasmatic fibrinogen, reactive C protein) at that moment. The immunological available tests also yielded normal results (rheumatoid factor, cryoglobulins, antinuclear antibodies, anti-Ro and anti-La antibodies, lupus anticoagulant, seric immunelectrophoresis). The screening for possible infectious etiologies was also not relevant (total HIV antibodies Genscreen

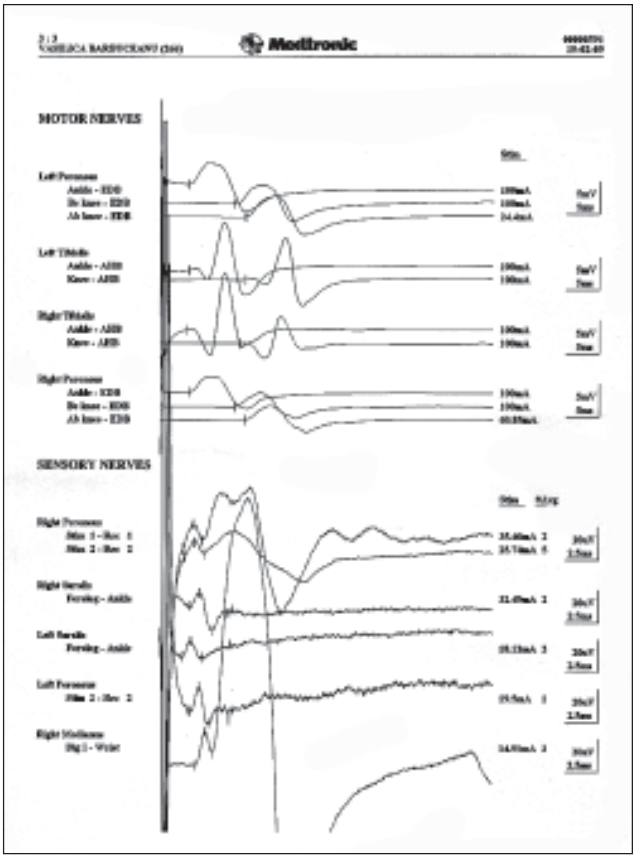

Figure 1. *Motor and sensitive conduction study. Lower than normal amplitudes of CMAP and SNAP in certain nerves in a random pattern (axonal multiplex mononeuropathy)*

negatives, total HIV 1 + 2 Murex antibodies negatives, negative serology for an acute/subacute infection with species of Borrelia, HTLV-1, B and C viral hepatitis, CMV, VZV, Leptospira, Toxoplasma, Trichinella). Seric ferritin remained constantly high. Her seric B12 vitamin levels were normal. A screening for porphyria yielded normal results (delta-aminolevulinic acid 3.7 mg/l, porphobilinogen 0.8 mg/l, coproporphyrines 41microgr.l, uroporphyrines 10 microgr/l). Tumoral markers were absent. She had a micropolinodulary, normal sized thyroid gland with euthyroidism. She had no history of alcohol consumption or exposure at toxic professional or environmental factors or drugs.

The sural nerve biopsy was performed at approximately 8 weeks from the disease onset. The nerve fragment underwent hematoxilin-eosin and trichrom Gomori staining on frozen section, epon inclusion with semithin sections and teased fibers study. The nerve biopsy suggested a chronic axonal neuropathy of inflammatory type with low density of myelinated axons (2229.5/mm^2, normally between 7000-11000/mm^2), with conserved normal bimodal distribution of large and small

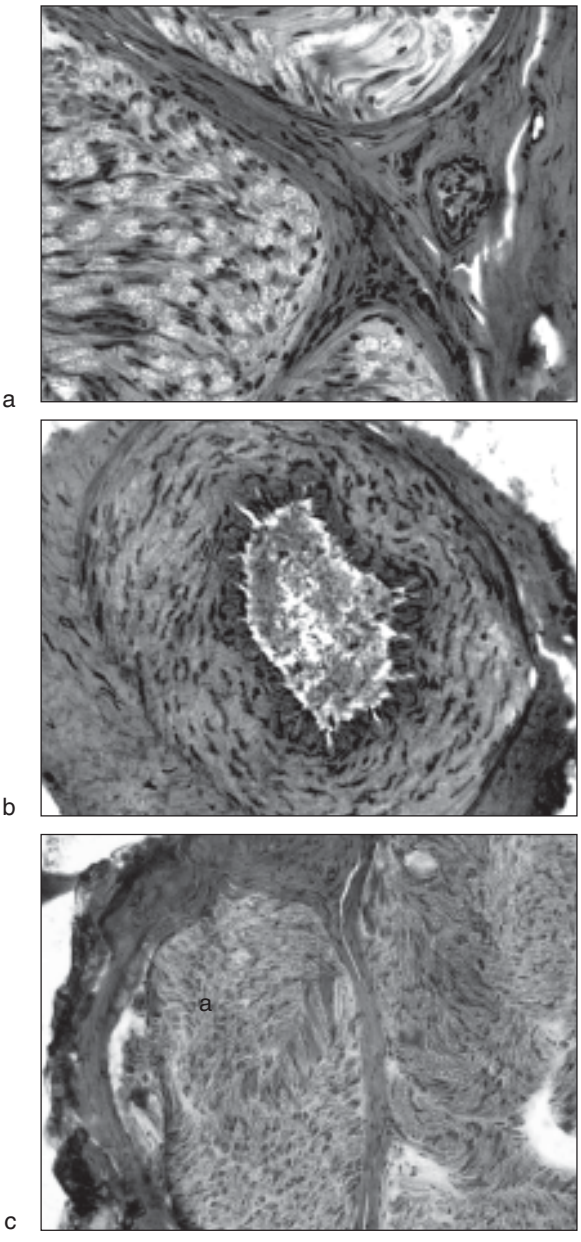

Figure 2. *Nerve histological studies: A and B – Hematoxylin-eosin staining, C – Trichrom-Gomori staining. In panels A and B a normal histological structure and normal fiber caliber and distribution are seen. Panel B and the asterix in panel A show an ubnormal thickening of vessels in vasa nervorum.*

caliber fibers. There were 2% dissociated myelinic fibers, with myelinic ovoids and 6% of teased axons were regenerating axons. Very small blood vessels had normal aspect, but some of the larger ones had enlarged arterial walls. There was no evident inflammatory infiltrate.

Because the biopsy results were available with an expected delay, a vitamin B group and a-lipoic acid oral therapy was initiated; concomitantly the patient received a short trial of deferoxamine followed by regular (initially weekly, afterwards at 2 weeks interval) therapeutic phlebotomies. At 6 months, the patient had a marked clinical and

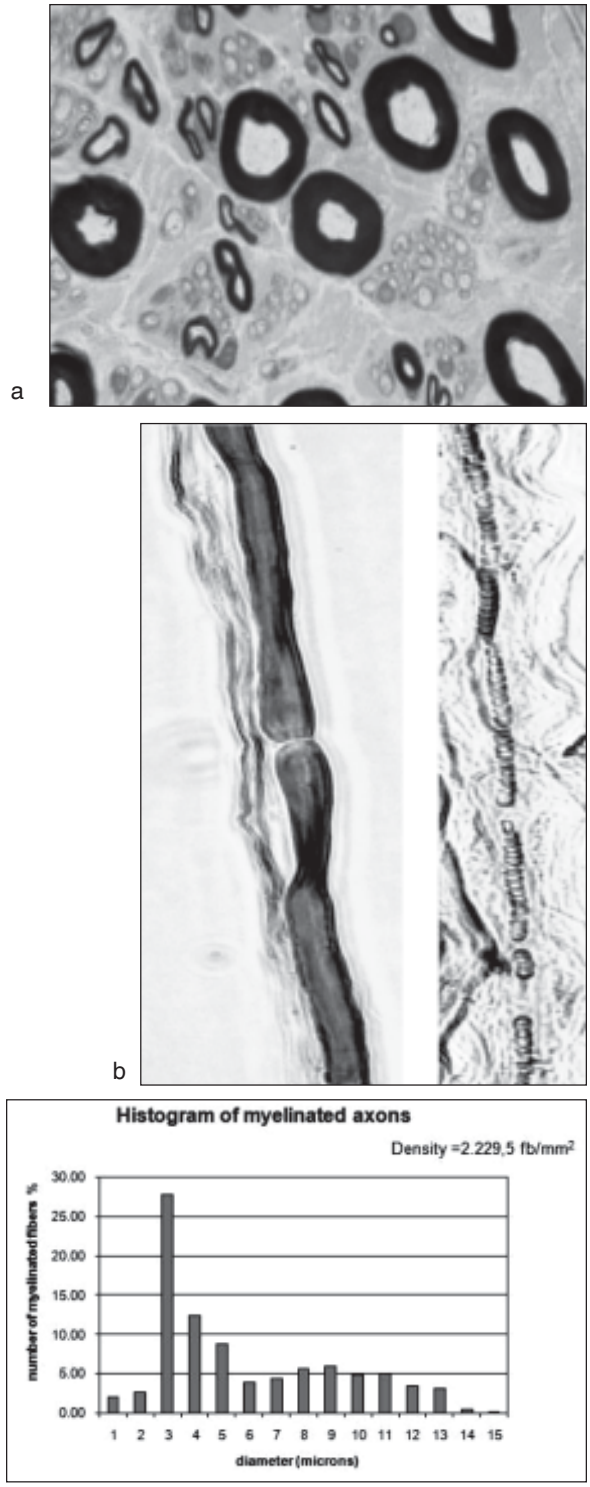

Figure 3. *Electronic microscopy nerve fibers study and quantification. A. Semifine transversal nerve section visualising myelinated axons; some fibers have thinner myelin sheats, suggesting axonal regeneration. B. Teasing image of nerve fibers. There are no segmental demyelination or nodal pathology. C. Histogram of myelinated axons shows low density of myelinated axons (2229.5/mm², normally between 7000-11000/ mm²) with conserved normal bimodal distribution of large and small caliber fibers.*

electrodiagnostic improvement (motor amplitudes slightly reduced peroneal bilateral with normal

conduction velocities, sensitive velocities of left median nerve slightly reduced). There was a marked improvement in the general tonus of the patient, with less fatigue, normal hepatic biochemistry and no anemia after repeated phlebotomies.

DISCUSSION

We report the case of a 59-year-old woman with an acute onset, subacute evolution of a mononeuropathy multiplex of axonal inflammatory type, with monophasic temporal profile (until now) and favourable outcome, that supervened in a moment when a systemic illness was recognised.

Ascertaining an etiology to all this findings was not an easy task.

The hereditary hemochromatosis diagnosis itself was a challenge in the absence of pertinent genealogical data. Seric ferritin is an acute phase reactant which elevates in various acute and chronic inflammatory states, alcoholism, chronic hepatopathy. Still, the repeatedly high seric ferritin with normal sideremia and transferrin saturation is compatible with type 4 of hereditary hemochromatosis (ferroportin disease), which is more prevalent in the Southern Europe, has a milder clinical picture and can be evident in postmenopausal women. Absence of viral etiology for chronic hepatitis, presence of arthralgia, left ventricle hypertrophy, diabetes in a mild form and also the good clinical response and the absence of anemia after repeated phlebotomies points to the diagnosis. Hemochromatosis by itself is not known to be associated with neuropathy otherwise than through the presence of diabetes.

Diabetes mellitus is well known for its potential of damage to the peripheral nervous system, beginning from latent stages. Even if the glycemic control of this patient was satisfactory, a diabetic neuropathy is not impossible. Still, the acute onset in the absence of significant glycemic oscillations or weight loss, the asymmetric pattern of involvement and the absence of significant pain made improbable a diagnosis of one of the two forms of diabetic neuropathy with acute onset, diabetic neuropathic cachexia and insulin neuritis.

Acute motor and sensitive axonal neuropathy syndromes are immune-mediated neuropathies with mono- or policlonal antibodies raise. Immunelectrophoresis was normal for this patient; immunofixation electrophoresis was not available. There was no evident cancer, no CNS involvement; even if there was marked asymmetric sensitive symptomatology, there was also motor peripheral involvement that made a anti-Hu positive subacute sensory neuronopathy improbable. An incomplete POEMS syndrome has polyneuropathy and organomegaly, endocrinopathy with diabetes but with symmetric, predominantly demyelinating neuropathy of slow onset and evolution. Cryoglobulinemia associates frequently hepatosplenomegaly, arthralgias, Raynaud phenomens, hypertension and a multifocal mononeuropathy, but cryoglobulins and hepatitis C virus were repeatedly negative in this patient.

The infectious etiologies were also precluded by screening for HIV, HTLV-1, Lyme disease, VZV, CMV.

Alcohol and other toxic drug and environmental toxicities were excluded by anamnesis.

A paraneoplastic etiology was improbable, there was no evident cancer and seric tumoral markers were absent.

Sarcoid neuropathy can sometimes embrace a clinical picture of multiplex mononeuropathy. The diagnosis is difficult, especially when the systemic disease is not yet recognised. The absence of pulmonary infiltration, bilateral hilar adenopathy, ocular or cutanate involvement, as well as the nonfluctuating pattern of neuropathic deficits and the absence of granulomas on nerve biopsy are not sustaining this hypothesis.

The most frequent cause of a multiplex mononeuropathy is a vasculitic process, either independent or within a connective tissue disease. The clinical presentation was typical: acute onset of multifocal neuropathy with both sensitive and motor involvement.

Systemic vasculitis associated with neuropathy have all general signs that cannot be overlooked, either there is a systemic necrotizing vasculitis, a hypersensitivity vasculitis or a vasculitis associated with a direct infection.

From the group of connective tissue disorders, the most frequent is rheumatoid arthritis. Our patient had evidence of vasculitic neuropathy without entrapment compression, with arthralgia but without morning stiffness or characteristic deformities, raised ESR or rheumatoid factor and no signs of systemic vasculitis. Also, nerve biopsy showed no arterial thrombosis, neovascularisation or segmental destruction of arterial walls.

Five to ten per cent of Sjögren syndrome patients develop a vasculitic neuropathy of asymmetric, axonal quality, with a predominance of sensitive symptoms. Our patient had no sicca syndrome, no autonomic dysfunction suggestive of dorsal root ganglionitis and no specific autoantibodies (anti-Ro,

anti-La, ANA, RF). Knowing that in 1/3 of patients neuropathy can precede Sjögren syndrome by 24 months, and considering the presence of arthralgia (even if they can be also explained by hemochromatosis) and Raynaud phenomenons in this patient, the diagnosis cannot be excluded at this point in time.

At onset, a patient can have only one or two manifestations of the polymorphic clinical picture of LES, but neuropathy occurs usually in the setting of established disease, with suggestive cutaneous, renal, pulmonary disease and a systemic vasculitis, which are all absent in our patient.

The neuropathy in sclerodermia is tipically predominantly motor, with much less sensitive involvement and a typical fingers appearance.

Except for trigeminal sensory neuropathy, other neuropathies are rare in mixed connective tisuue disease and are generally symmetrical.

None of the above mentioned vasculitis can be excluded with certainty for our patient in the absence of the probe of time, but they are improbable on the basis of actual information.

An isolated, nonsystemic peripheral nerve vasculitis is the most common encountered cause of vasculitic neuropathy in clinical practice. As most of patient's non-neurological symptoms could be ascertained to hemochromatosis, we can with relative certainty to assume that, in the absence of this disorder, the patient would present with signs and symptoms isolated to the peripheral nervous system. Finding involvement of small and medium-sized arteries on the biopsy is an argument for this; finding a necrotizing arteritis in muscle biopsy would be a stronger one, but the diagnosis remaines an exclusion one.

Finally, the therapeutic probe can add information on diagnosis. We regard the favourable evolution of this patient more as a part of the natural evolution of the disease than as a result of the nonspecific treatment applied. It is probable that repeated phlebotomies improved diabetes and so the glycemic control, that led by itself to a lower general peripheral nerve susceptibility to different aggressions, irrespective of their nature.

CONCLUSION

Etiological diagnosis of a peripheral neuropathy remains an extremely challenging work-up even in the 21st century, despite significantly improved access at thorough investigations.

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