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ABSTRACT

In this paper we discuss the case of a small-fiber neuropathy patient with heterozygous gene mutation, a single-nucleotide sequence variation c.353C>T in peripheral myelin protein 22 (PMP22) gene. The patient was diagnosed with a current infection with Coxsackie virus, herpes simplex virus type 1 (HSV-1) and 2 (HSV-2), as well as a previous infection with human herpesvirus 3 (HHV-3 or varicella-zoster) and 4 (HHV-4 or Epstein-Barr). We also discuss the diagnosis and therapy of patients with small-fiber neuropathy. With regard to etiology, future studies must clarify if viruses are causing small-fiber neuropathy directly through lytic replication or indirectly through release of viral proteins and neurotoxic substances from macrophages. The efficacy of antiviral drug treatment in infectious small-fiber neuropathy needs clarification.

KEYWORDS: Small-fiber neuropathy, PMP 22 gene, Coxsackie virus, HSV-1, HSV-2, HHV-3, HHV-4, acyclovir, artemisin, clinoptilolite.

INTRODUCTION

Small-fiber neuropathy is a peripheral degenerative axonopathy that occurs from small nerve fibers damage (A delta and C). Group A delta are thinly myelinated fibers that carry information relating to sharp pain, cold and pressure. Group C are unmyelinated fibers that carry information relating to burning pain, warmth and itch (1). Overall incidence of the disease is not known (2). The economic burden of the disease in the United States only was estimated at over 21000$/patient/year (3). Causes of small-fiber neuropathy are metabolic (e.g. diabetes), infectious (e.g. human immunodeficiency virus), medication (e.g. metronidazole), immune-mediated (e.g. celiac disease), hereditary (e.g. sodium channelopathies), syndromic (e.g. fibromyalgia, Parkinson's disease, amyotrophic lateral sclerosis) and idiopathic. The molecular mechanism of the disease is not clear, but there is evidence that neurotoxic substances released by macrophages (e.g. cytokines, chemokines and glutamates) and mitochondrial dysfunction due to metabolic stress (e.g. hyperglycemia and dyslipidemia) play a significant role in the pathogenesis of small-fiber neuropathy. Diagnosis is based on clinical history and neurological examination, main symptoms are burning pain, numbness, loss of thermal sensation an pruritus, starting in feet and hands, and progressing proximally in a “stocking-glove” distribution, and confirmed by intraepidermal nerve fiber density assessment from ankle skin biopsy (4). Treatment is symptomatic and focuses on decreasing neuropathic pain using gabapentinoids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors and topical anesthetics or analgesics (5).

Clinical studies that investigate the use of intravenous immunoglobulin as a possible pathogenetic treatment are currently performed (6). Disease evolution is slow-progressing, with non-length-dependent distal axon loss (7).

Patient history

A 19-year-old woman with a clean past medical history had in 2012 left big toe joint pain and bilateral plantar cramps. Symptoms disappeared without any medical treatment. Two years later, after a throat infection, the patient had burning tongue, muscle, joints and skin pain in the lower, then upper limbs, neck and shoulder. A chronic pain syndrome was diagnosed in a neurological private practice. Although the neurologist prescribed gabapentin, buprenorphine and carbamazepine, the patient discontinued treatment due to lack of efficacy. In 2015 the patient was admitted in a neurological hospital for further diagnosis. At hospital admission the patient complained about burning tongue and multiple joints pain.

A standard laboratory blood test (i.e. sodium, potassium, urea, gamma-glutamyl transferase, hemoglobin, hematocrit, international normalized ratio, creatinine, mean corpuscular hemoglobin concentration, mean corpuscular volume, activated partial thromboplastin time, thrombocytes, erythrocytes, leucocytes, creatine kinase, calcium, lactate dehydrogenase, glutamic oxaloacetic transaminase, hemoglobin A1c and thyroid stimulating hormone) showed normal values.
A magnetic resonance imaging total-spine examination showed no pathological findings. A histological examination of skin biopsy revealed a pronounced rarefaction of epidermal nerves, as seen in small-fiber neuropathy. A quantitative sudomotor axon reflex test (QSART) showed reduced sweat output and increased latency of sweat response in all limbs, indicating a postganglionic disorder. A temperature sensation test showed thermhypalgesia for warmth at all measuring sites, for cold at the upper and lower left limb, and thermhypalgesia for warmth at the upper left limb.

A genetic test showed a heterozygous gene mutation, a single-nucleotide sequence variation c.353C>T in peripheral myelin protein 22 (PMP22) gene. Large-fiber neuropathy, hereditary motor-sensory neuropathy (HMSN) type 1 and 2, hereditary neuropathy with pressure palsies (HNPP), multiple sclerosis, Fabry disease and rheumatic diseases were diagnostically excluded. The patient refused any drug treatment and was discharged from hospital. In 2016, upon suspicion of borreliosis due to multiple joints pain, left-sided ear and facial pain, the family physician prescribed tinidazole, amoxicillin and minocycline tablets for five months. Symptoms did not improve.

Due to worsening of symptoms in 2017 a bacterial and viral blood test was done. Lymphocyte count showed lymphocytopenia for CD3+ with 22/µl (100-360), thus indicating a viral infection, and CD57+ with 877/µl (900-1900), thus indicating a chronic infection. Coxsackie IgG type A7 (immunofluorescence-IFT) was positive at over 1:100 (<1:100), IgG type B1 (IFT) was positive at over 1:100 (<1:100), IgA type A7 (IFT) was positive at over 1:10 (<1:10) and IgA type B1 (IFT) was positive at over 1:10 (<1:10).

Herpes simplex virus type 1 (HSV-1) and 2 (HSV-2) IgM were slightly increased at 0.960 Ratio (<0.8 negative, 0.8-1.1 borderline, >1.1 positive). Human herpesvirus 3 (HHV-3 or varicella-zoster) IgG was positive at 3122.5 IE/l (<80 negative, >80-<110 borderline, >110 positive). Human herpesvirus 4 (HHV-4 or Epstein-Barr) IgG (IFT) was positive (negative), EA (IFT) was positive (negative), EBNA-1 IgG was positive (negative) and avidity was high (low). A current infection with Coxsackie virus, HSV-1 and HSV-2, as well as a previous infection with HHV-3 and HHV-4 were diagnosed. The patient was admitted one year later to our clinic for neurological rehabilitation because of exacerbated symptoms. The clinical examination showed disturbed temperature perception, generalized paresthesia, neuropathic pain in all limbs, balance disorder and nausea.

The patient had 8 points on the pain scale (0-12), thus indicating a high chance of small-fiber neuropathy (8). A Barthel activity of daily living index was 100 points (0-100). A standard laboratory blood test was done. The value of C-reactive protein (CRP) 1.45 mg/dL (<0.60) was increased. After obtaining informed consent (GOLUP), the patient received off-label intravenous acyclovir via superficial vein catheter (once 125 mg on day 1, twice 250 mg on day 2, three times 250 mg on day 3, three times 500 mg on day 4, four times daily 500 mg on days 5-30). Routine laboratory examinations once weekly after starting antiviral treatment showed normal serum creatinine, normal glomerular filtration rate (GFR) and normal blood urea nitrogen.

Acyclovir was well tolerated, only nausea occurred as a side effect on days 15-16, which did not require discontinuation of treatment. The injection site (right and left median cubital, basilic, cephalic and radial veins) was changed as clinically indicated, every 3 days on days 1-15 and every 1.5 days on days 16-30. In spite of that, the patient developed a superficial vein thrombosis at the right elbow on day 25, which required symptomatic treatment.

The patient was also treated on-label per os with two natural products: Artemisia annua 400 mg once daily and Froximun toxaprevent 400 mg twice daily for 6 weeks, followed by a therapy break of 5 days. These products were well tolerated. The patient received physiotherapy. At hospital discharge the patient was prescribed off-label oral acyclovir 800 mg five times daily for 3 weeks, followed by 400 mg five times daily for 3 weeks and on-label Froximun toxaprevent 400 mg twice daily for 6 weeks with a therapy break of 5 days after day 30 (9).

Discussions

The PMP22 gene is located in humans on chromosome 17. The PMP22 gene encodes peripheral myelin protein 22, a transmembrane glycoprotein expressed in Schwann cells of the peripheral nervous system, which helps nerves restore their structure after physical compression. PMP22 gene point mutations are causing hereditary motor-sensory neuropathy (HMSN) and hereditary neuropathy with pressure palsies (HNPP) (10). There are no published case reports and there is no evidence in the medical literature suggesting that PMP22 gene point mutations are causing small-fiber neuropathy. Damage of small nerve fibers as a result of infections with Coxsackie virus, HSV-1, HSV-2, HHV-3 or HHV-4 has not been reported.
Coxsackie virus infection does not release cytokines from macrophages (11). HSV-1, HSV-2 and HHV-3 activate the release of cytokines from macrophages (12). HHV-4 inhibits the release of cytokines from macrophages (13). However, HHV-4 has the ability to infect in vitro human neurons (i.e. neuroblastoma, teratocarcinoma and fetal). Human neurons were exposed in vitro to genetically modified HHV-4 that expressed green fluorescence protein (EBV-GFP). After 24 hours, viral gene expression increase was monitored for 9 days post-infection using a quantitative polymerase chain reaction (qPCR) assay. At the same time, cellular morphology changes and lysis were observed using fluorescence microscopy.

After 48 hours, cells that were treated with acyclovir had a lower viral gene expression determined by qPCR assay and a lower lysis rate seen on fluorescence microscopy, thus suggesting lytic replication in neurons (14). Acyclovir is a nucleoside analogue antiviral drug that inhibits replication of HSV-1, HSV-2 and HHV-3 without affecting replication of human cells. This selectivity is the result of higher drug affinity for viral polymerase as compared to that for human polymerase (15). Dosage in adults is 10-15 mg/kg ideal body weight intravenous every 8 hours for 10 days or 200-800 mg oral five times daily for 7-10 days, depending on immune status and disease (Acyclovir SmPC). Off-label use of drugs in a treatment regimen (in this case acyclovir dosage and duration) other than that listed in the Summary of Product Characteristics (label) is tolerated in the European Union as part of therapeutic freedom (16).

Long-term intravenous therapy with acyclovir up to 21 days with 10-15 mg/kg ideal body weight every 8 hours in herpes and varicella encephalitis is well tolerated by patients (17). Long-term oral therapy up to 12 weeks with 200 mg acyclovir four times daily in recurrent genital herpes is also well tolerated by patients (18). Short-term oral therapy for 7 days with 800 mg acyclovir five times daily in adult varicella is safe (19).

Acyclovir therapy is effective in reducing pain in patients with herpes simplex and varicella infections (20). In patients with Epstein-Barr virus infection acyclovir treatment has no efficacy (21). According to clinical studies, side effects were similar in frequency for patients randomized to oral acyclovir or placebo and included nausea, diarrhea and headache (22). Most common side effects in intravenous acyclovir therapy are phlebitis at the injection site, serum creatinine increase and urticaria (23). Routine versus clinically indicated replacement of peripheral venous catheters does not decrease the frequency of side effects (24). Due to its pH of approximately 11, acyclovir is venous irritant (25). This is why acyclovir should be administered whenever possible through a central venous catheter (26).

If intravenous therapy with acyclovir is not possible, oral therapy with acyclovir's prodrug valacyclovir 1000 mg three times daily for up to 21 days is safe and effective in herpes simplex encephalitis (27), but its usefulness in small-fiber neuropathy is unclear. Increased ambulatory compliance to oral treatment with nucleoside analogues can be obtained by switching from acyclovir 800 mg five times daily to famciclovir 250 mg three times daily for up to six weeks (28). Artemisia annua is a herb used in traditional Chinese medicine. Its main active component, artemisin, is effective mainly against parasites (e.g. malaria, schistosoma) and cancers (e.g. liver, colon) (29). Artemisin is effective against viruses of Herpesviridae family (e.g. HSV-1 and HHV-4) by inhibiting cellular signaling pathways used by viruses for replication (30).

The recommended dosage is 400 mg once daily, but the duration of therapy is not specified (31). Long-term therapy for 6 months with Artemisia annua extract 150 mg twice daily is safe (32). The active ingredient of Furoximun toxaprevir is clinoptilolite, a natural zeolite. This aminosilicate mineral has ion exchange properties and binds ammonium, heavy metals and histamines in intestine (33). Clinoptilolite inhibits viral replication of HSV-1 and Coxsackie virus in vitro probably by incorporating viral particles into pores of micronized zeolite (34). Dosage recommendations are 400 mg twice daily for 30 days, followed by a therapy break of 5 days (35). The safety of clinoptilolite in long-term therapy has not been investigated by clinical studies.

Future studies must clarify if viruses are causing small-fiber neuropathy directly through lytic replication or indirectly through release of viral proteins and neurotoxic substances from macrophages. In vitro studies must verify if Coxsackie virus has the ability to infect human neurons (i.e. neuroblastoma, teratocarcinoma and fetal) and cause small-fiber neuropathy directly through lytic replication. Molecular studies must also clarify if cytokines released from macrophages activated by HSV-1, HSV-2 and HHV-3 are causing small-fiber neuropathy. Clinical studies must verify if etiologic therapy with acyclovir, artemisin and clinoptilolite is effective in reducing the progression and symptoms of infectious small-fiber neuropathy, establish dosage and treatment duration, as well as safety in long-term therapy. Successful drug therapy could reduce the economic burden of the disease.

**Conclusions and future perspectives**

Future studies must clarify if viruses are causing small-fiber neuropathy directly through lytic replication or indirectly through release of viral proteins and neurotoxic substances from macrophages. In vitro studies must verify if Coxsackie virus has the ability to infect human neurons (i.e. neuroblastoma, teratocarcinoma and fetal) and cause small-fiber neuropathy directly through lytic replication. Molecular studies must also clarify if cytokines released from macrophages activated by HSV-1, HSV-2 and HHV-3 are causing small-fiber neuropathy. Clinical studies must verify if etiologic therapy with acyclovir, artemisin and clinoptilolite is effective in reducing the progression and symptoms of infectious small-fiber neuropathy, establish dosage and treatment duration, as well as safety in long-term therapy. Successful drug therapy could reduce the economic burden of the disease.

**Conflicts of interest**

The author has no conflicts of interests that are directly relevant to the content of this manuscript.

**Disclosure**

No sources of funding were used to assist in the preparation of this manuscript.
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**Citation:** Dr. Septimiu Tudor Bucurescu., “Small-fiber neuropathy in a patient with PMP22 gene single-nucleotide sequence variation, Coxsackie virus, HSV-1, HSV-2, HHV-3 and HHV-4 infection: A case report”. American Research Journal of Neurology, Volume 4, Issue No. 1, 2021, pp. 1-5.

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