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Case report/Kazuistyka

Bilateral peripheral facial palsy secondary to Waldenström's macroglobulinemia. A case report and literature review

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ABSTRACT

A 59-year old woman who attended the emergency department because of a bilateral peripheral facial nerve palsy (FNP). Bilateral FNP is uncommon, an idiopathic cause is unlikely and consequently a comprehensive study is indicated. An IgM monoclonal gammopathy was detected on serum protein electrophoresis of our patient. Bone marrow biopsy showed the presence of lymphoplasmocytoid cells. On the basis of these findings the diagnosis of Waldenström's macroglobulinemia (WM) was made. Secondary cranial nerve palsies are rarely seen in this condition. This report describes a case of bilateral FNP as initial presentation of a Waldenström's macroglobulinemia and discuss treatment.

Introduction

Idiopathic facial nerve palsy (FNP), or Bell's palsy, is the most prevalent acute disorder affecting the seventh cranial nerve with an incidence of 20–30 patients per 100 000. Conversely, bilateral FNP is rare, representing less than 2% of all the facial palsies and affecting five patients per 100 000. Most of these patients have serious underlying medical conditions and need to be evaluated carefully [1].

Waldenström's macroglobulinemia (WM) is a rare low-grade B-cell lymphoma characterized by involvement of the reticuloendothelial system by lymphoplasmacytoid cells which secrete monoclonal IgM. Uncontrolled production of this immunoglobulin increases serum viscosity and causes tumor cell infiltration of the tissues. Up to 47% of patients with WM develop symptomatic peripheral neuropathy but cranial nerve palsies are rare in this condition [2]. We describe a case of WM presenting as bilateral FNP.

Case report

A 59-year old lady attended the emergency room presenting symptoms of left facial numbness and weakness, inability to close her left eye and asymmetry of the mouth. The

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patient was diagnosed as a left Bell's palsy and treatment with prednisone 30 mg three times a day was prescribed. Two days later, she returned because of worsening symptoms; the facial weakness became bilateral and she had secondary dysarthria. Examination revealed bilateral lower motor neuron FNP (Fig. 1). The rest of the neurological examination was unremarkable. The patient had no medical history of interest, except for a recent trip to Kenya and Tanzania, where she referred a mosquito-bite. She had taken antimalarial prophylaxis with proguanil correctly.

The complete blood count, biochemical analysis, chest X-ray and head computer tomography were normal. The patient was hospitalized under the care of the neurology department with the suspect of bilateral Guillain-Barré syndrome. She started treatment with intravenous corticosteroids and oral doxycycline until Lyme disease was ruled out.

Lumbar puncture revealed proteinorrachia (463 mg/L) and an increase of IgM index (0.23), adenosine deaminase (5 μ/L) and neuron specific enolase (35.1 ng/ml). Serological tests for various agents including *Borrelia burgdorferi* (Lyme disease), syphilis and Epstein-Barr virus were negative. Likewise, the culture of cerebrospinal fluid and tumor cytology were both negative.

Head magnetic resonance imaging (MRI) showed bilateral asymmetrical enhancement of the facial nerves, with left-sided predominance.

Nerve conduction studies showed no alteration of peripheral nerve conduits, consequently Guillain-Barré was ruled out. At that time, facial electroneurography (ENG) was inconclusive, while a month later, it revealed a mixed lesion: axonal and demyelinating with more severe affection of the left side.

A monoclonal IgM spike was detected in serum protein electrophoresis with an increased level of β_2-microglobulin. Bone marrow biopsy revealed nodular intertrabecular infiltration by a low grade B non-Hodgkin lymphoma. The immunophenotype profile of the lymphoplasmocytoid cells was CD20+, CD3−, CD5−, CD23−, bcl-6- and CD10− consistent with the diagnosis of WM. The patient received six cycles of ambulant systemic chemotherapy and immunotherapy based on DRC-scheme: dexamethasone, rituximab (375 mg/m^3) and cyclophosphamide, spaced over eight weeks. Treatment with artificial tears and ointment and eye patching during night was prescribed because of the high risk of exposure keratopathy.

Three months later, the demyelinating component recovered on ENG and reinnervation of both facial nerves began. Improvement correlated with a dramatic decrease in IgM levels, antibody titles and circulating B cells. Lagophthalmos (inability to close the eyes) improved and, ophthalmological examination showed only mild punctate superficial keratopathy in the left eye.

Nine months after diagnosis, IgM levels have declined more. The patient presents a mild facial asymmetry with absence of lagophthalmos in both eyes (Fig. 2), the smile was restored and the nasolabial fold has been corrected. The electromyogram (EMG) shows an improvement of both facial nerve reinnervation and functional recovery especially of the orbicularis oculi muscle and the lips. As well, a moderate increment of the motor activity could be detected.

Aberrant reinnervation was demonstrated by EMG, clinically expressed by sinkynesis, and a pathological spread of the reflex response of both facial nerves to unusual territories, especially on the left side.

The patients will continue treatment with rituximab-cycles every eight weeks until two year completion.

Discussion

Bilateral FNP is an infrequent disease and a serious underlying medical condition should be suspected. Possible causes include infectious, autoimmune and metabolic diseases, tumors, toxic and congenital disorders. There are several viral and bacterial agents which can produce bilateral or recurrent FNP. Lyme disease, caused by spirochete *Borrelia burgdorferi*, is the most common infectious etiology, followed by Epstein-Barr virus. Guillain-Barré Syndrome (inflammatory post-infectious polyradiculoneuritis) is another important cause of bilateral FNP to be ruled out, because up to 50% of fatal cases can occur. As well, intrapontine and prepontine tumors should be excluded. There is one reported case of bilateral FNP and acute myeloid leukemia [3].

WM is considered an indolent form of B-cell non-Hodgkin lymphoma, also known as lymphoplasmocytic lymphoma by the World Health Organization (WHO) classification.

Infiltration by lymphoplasmacytic cells, predominantly of the bone marrow together with an IgM monoclonal gammopathy, is considered a diagnostic finding [4]. WM accounts for 1–2% of all hematologic malignancies and in terms of

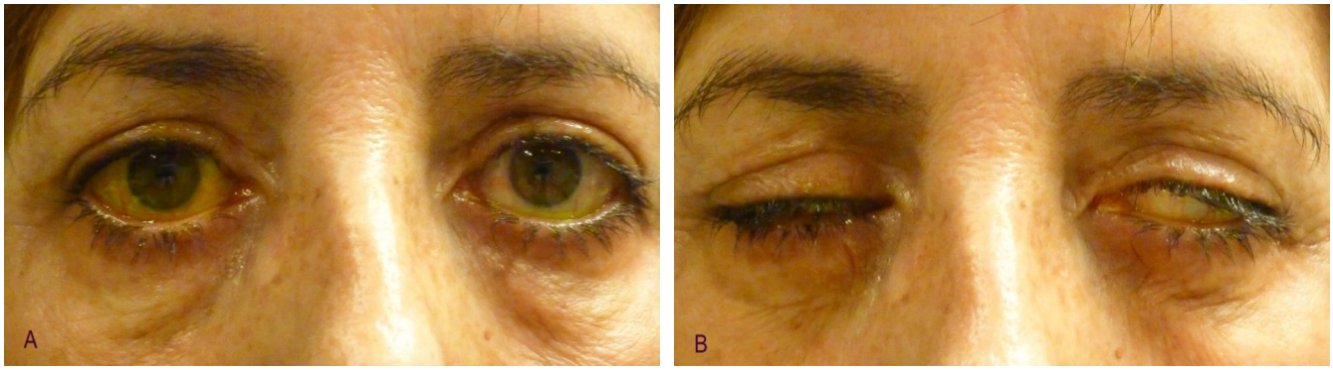

Fig. 1 – The patient ten days after facial palsy. Inability to close both eyes, specially the left

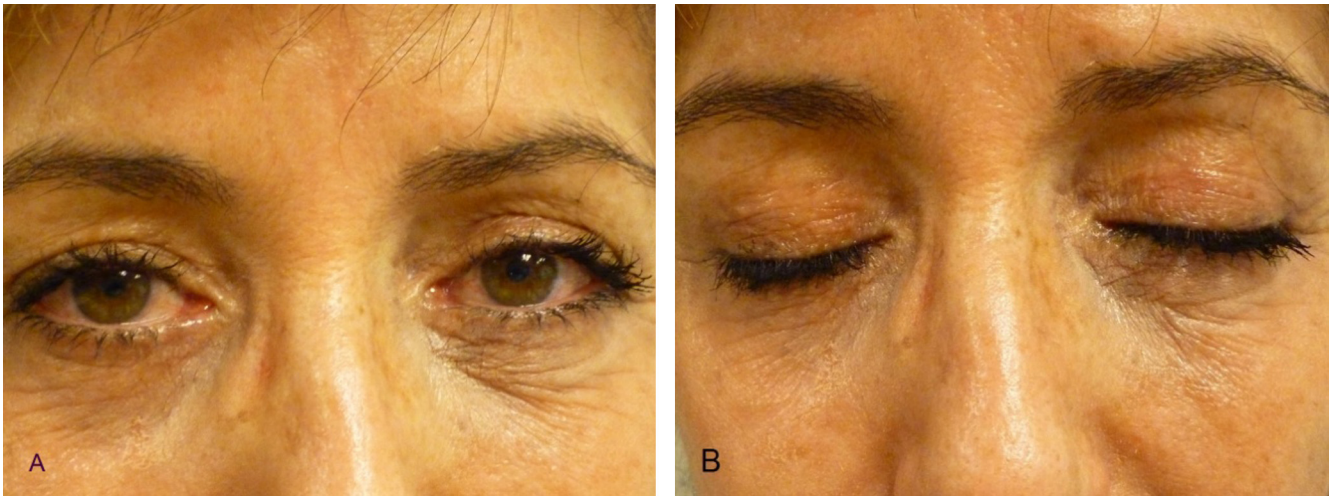

Fig. 2 – The patient nine months after facial palsy. Recovery of lagophthalmos and occlusion of both eyes

pathogenic evolution, the condition straddles between monoclonal gammopathy of unknown significance (MGUS) and multiple myeloma. The disease most commonly affects men above 60 years of age. Typically manifestations are diffuse lymphadenopathies, cytopenias and a markedly elevated erythrocyte sedimentation rate. Clinical symptoms are due to the monoclonal IgM protein, tissue infiltration by the lymphoplasmocytic cells, or both [5]. Hyperviscosity retinopathy is the most common ocular abnormality reported in WM [6]. Peripheral neuropathy (PN) is a frequent complication of IgM monoclonal gammopathy, occurring in 15–30% of patients with either MGUS, most commonly, or WM.

Of the whole spectrum of peripheral neuropathies, the typical pattern consists in a chronic progressive symmetric and predominantly distal polyneuropathy, but also other symmetric polyneuropathies, cranial nerve palsies, mononeuropathies and mononeuritis multiplex. Isolated cranial neuropathies are rare in WM [2]. About 25% of patients with WM suffer from central nervous system (CNS) symptoms secondary to increased blood viscosity (Bing-Neel syndrome) leading to anoxic damage and hemorrhages of the brain tissues. In the context of CNS involvement cranial nerve palsies are more common. We found a case report of bilateral sixth nerve palsy in a patient with Bing-Neel syndrome [7]. To our knowledge there is no case report about facial diplegia secondary to this entity. Moreover, during literature review we have only found one report of isolated trochlear nerve palsy [8], another of unilateral facial nerve palsy [9], in the absence of other nervous system manifestations.

IgM has been found to have anti-nerve antibody activity. The most frequently reported antigen recognized by this monoclonal IgM is myelin-associated glycoprotein (MAG). The mechanism by which anti-MAG enters the nerve and causes demyelination and neural damage is unclear. Other neural antigens have also been associated with polyneuropathies including several anti-gangliosides (antiGM1), sulfatide and tri-sulfated heparin disaccharide [10]. Non-antibody-mediated mechanisms have also been implicated in patients without antineural reactivity of IgM paraprotein: cryoglobulinemia, direct lymphoplasmacytic infiltration of the nerves, and vasculitis.

Anti-gangliosides and anti-sulfatides were not detected in our patient but anti-MAG were positive, so we think, that in our case the mechanism involved was autoimmune. In addition, improvement of the FNP after rituximab and corticosteroids supports the antibody mediated response rather than tumoral nerve infiltration.

A watch and wait strategy is recommended in asymptomatic patients with WM (almost a third of them), with periodic examinations every six months.

Administration of intravenous immunoglobulin is one of the most commonly used first-line therapies for anti-MAG antibody associated polyneuropathy in MGUS. The treatment seems to provide short-term benefit, although data from prospective long-term studies are unavailable [11]. It seems reasonable to provide this treatment to patients with WM and IgM-related neuropathy, in conjunction with tumor-directed treatments. As per the previous recommendations of IWWM-4, dexamethasone, rituximab, and cyclophosphamide (DRC) remains the primary choice. Rituximab is a chimeric antibody that targets the B-cell antigen CD20 (375 mg/m^3 weekly for 4 weeks). Further doses or maintenance schedules can be considered [12]. A consensus panel has recently updated treatment for WM [13]. The treatment of IgM-related neuropathy may initially involve a course of plasmapheresis, especially in symptomatic patients with an aggressive course and circulating antibodies against peripheral nerve glycoproteins or lipids expected to receive rituximab. Systemic chemotherapy with rituximab improve sensory functions in several studies. Single-agent rituximab can be considered as the first intervention in patients with mild, slowly progressive neuropathy. In patients with severe or refractory disease, the combination of fludaravine (a nucleoside analog) and rituximab may be considered. Bendamustine/rituximab may achieve paraprotein reductions but there is limited experience in IgM-related neuropathy.

Our patient received treatment with chemotherapy and immunotherapy based on DRC-scheme with good response. Fludaravine-rituximab is effective but toxic, and DRC is safe. The identification of the somatic mutations MyD88 and CXCR4 offers the opportunity for a more targeted approach [14, 15].

Novel agents such as abrutinib, Ixazomib, oprozomib and obinutuzumab (GA-101) a new monoclonal anti-CD20 antibody recently approved, are being studied. A prospective, open-label, single stage, phase 2 study concludes that, carfilzomib (second-generation proteasome inhibitor), rituximab and dexamethasone (CaRD) offers a neuropathy-sparing approach for treating WM.

Autologous stem cell transplantation may be considered in young patients with chemosensitive disease and in newly diagnosed patients with very high-risk features.

In conclusion, although an idiopathic etiology is possible in bilateral FNP, efforts should be undertaken to identify a specific cause in each patient because some of the diagnostic possibilities are life-threatening and potentially fatal.

Update results from the phase 2 DRC study indicate that this is an effective strategy for many patients with WM and paraprotein-related neuropathy. For patients with short-lasting remission, progressive disease or resistance to a first-line therapy, second-line treatment with agents of different class, alone or in combination is indicated. Large, well designed randomized trials are required to establish more selective and safer immune-therapies for these neuropathies.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

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None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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