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Case Report

ANTINEURONAL ANTIBODY TESTING IN AN UNUSUAL CASE OF RECURRENT BELL'S PALSY

Egon Kurča[1], Zdeněk Kadaňka[2], Michal Drobný[1], Vladimir Nosál[1], Milan Grofik[1]

[1]Department of Neurology, Jessenius School of Medicine, Comenius University, Martin, Slovak Republic;
[2]Department of Neurology, School of Medicine, Masaryk University, Brno-Bohunice, Czech Republic

SUMMARY – The term Bell's palsy (BP) is nowadays reserved for peripheral facial nerve paralysis without well-defined etiology and pathogenesis. BP is not a life threatening condition but it has a potential cosmetic mutilatory effect, and there is also a possibility of serious ophthalmologic complications (corneal ulcers). Recurrent paralyses are noted in 7%-8% of BP cases. Only two patients with four BP episodes out of 1700 patients, and only one patient with more than four BP episodes out of 2414 BP cases have been reported in the literature. The highest number of BP recurrences found in the available literature is nine. A brief review of the epidemiology and etiopathogenesis of BP is presented, a case of unusual recurrent BP is reported, and the immune pathomechanisms are discussed.

Key words: *Bell palsy – etiology; Bell palsy – immunology; Facial paralysis – pathogenicity*

Introduction

Bell's palsy (BP), a cryptogenic facial nerve damage resulting in half-face mimic muscle paralysis, is known from ancient Egypt. It is not a life threatening condition but it has a potential cosmetic mutilatory effect, and there is a possibility of serious ophthalmologic complications (corneal ulcers) as well. We present a brief review of the epidemiology and etiopathogenesis of BP, and report on an unusual case of recurrent BP.

Epidemiology

The term BP is nowadays reserved for peripheral facial nerve paralysis without well-defined etiology and pathogenesis. The incidence of BP is still relatively high. Adour reports on up to 74% of idiopathic facial nerve paralysis[1], however, these data must have been influenced by the type of classification used and efforts invested to find the cause of neuropathy. Katusic *et al.* report on the average annual BP incidence in Rochester (Minnesota, USA) in 1968-1982 to be 25.0/100 000 inhabitants[2]. This rate is consistent with the results of epidemiologic analyses from other countries. There are isolated data on the regional and temporal BP clusters, which may point to infectious and environmental factors in the pathogenesis of BP (e.g., lower BP incidence in summer)[3]. Some authors point to frequent coincidence of BP with diabetes mellitus, late pregnancy, or early postpartal period. BP equally affects men and women, and its incidence is significantly lower under 19 and over 70 years of age. The disease onset during the first three decades of life is recorded in up to 50% of BP cases. A possible lower BP incidence in yellow people has been suggested by comparison between Western and Japanese studies[4]. Simultaneous bilateral BP (time delay between right and left BP onset shorter than 2 weeks) is relatively rare (0.7% - 1.2% of cases) and is sometimes an indicator of generalized neuropathy (e.g., Guillain-Barré syndrome, amyloidosis, leprous neuropathy)[5]. It is interesting that men prevail among these cases.

Correspondence to: *Assoc. Professor Egon Kurča, M.D., Ph.D.*, Department of Neurology, University Hospital, Kollárova 2, 036 59 Martin, Slovak Republic
E-mail: kurca@mfn.sk

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Repeated BP in one person merits attention. Recurrent paralyses are noted in 7% - 8% of BP cases[6]. Yanagihara *et al.*[4] report on a higher prevalence of unilateral BP recurrence in women under 19 years of age, however, there were no convincing sex differences in other studies. Paralysis recurrence in 10 years from the first BP episode is recorded in 70% of cases. The younger the patient with BP, the higher the probability of BP recurrence. Also, the probability of BP recurrence rises with total BP episode count. Adour has reported only two patients with four BP episodes out of 1700 patients[7]. Only one patient with more than four BP episodes in a cohort of 2414 BP cases has been described by Yanagihara *et al.*[4]. The highest number of BP recurrences found in the available literature is nine[8]. The interval between two BP attacks is usually more than one year. There is no side prevalence for BP recurrences. Ralli and Magliulo report on worse prognosis in cases with homolateral *versus* contralateral BP recurrence[9]. Other authors do not confirm this opinion[10]. In any case, the probability of complete functional recovery decreases with BP recurrence[11]. Diabetes mellitus and positive family history are considered to be independent risk factors for BP recurrence (the 31.3% prevalence of diabetes mellitus and 22.8% prevalence of first degree relatives with BP are 2.5-fold respective values found in patients with monophasic BP)[7].

Etiopathogenesis

The etiopathogenesis of BP has not yet been satisfactorily elucidated. Infectious (mainly viral) factors and immune mechanisms have been considered. Some information on direct herpes simplex virus 1 (HSV-1) involvement in BP genesis have emerged in recent years. HSV-1 deoxyribonucleic acid (DNA) sequences were found in facial nerve perineural fluid of patients with acute BP but not in the control group[12]. Latent HSV-1 ganglion geniculi infection reactivation with virion migration and subsequent local immune reaction seems to be the cause of intracanalicular facial nerve edema often resulting in its partial ischemic necrosis. HSV-1 DNA was also identified in the temporal bone of a patient who died 6 days after the onset of BP[13]. HSV-1 virus inoculation in the auricles and tongues of mice was used as a recent animal model of BP. Transient BP arises 6-9 days after virus inoculation[14]. Direct infectious or indirect parainfectious (e.g., molecular mimicry) mechanism with subsequent immune reaction involvement of tumor necrosis factor α (TNF-α) in the pathogenesis of BP has been confirmed) is highly probable in case of different herpetic viruses (cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV6), human herpesvirus 7 (HHV7)), adenoviruses, and other non-defined viral or bacterial agents. The existence of reflex vascular mechanism remains an open question. Ramsay-Hunt's external ear zone cooling may provoke transient facial nerve vasa nervorum spasm resulting in its ischemia, edema, loss of function, and eventually pathologic structural changes (cold palsy). The effect of cold on the immune system and possible manifested or latent infection is another aspect of 'cold palsy'. Congenital predisposition to BP due to narrow fallopian canal (mainly its medial part) has been repeatedly discussed.

Peripheral facial nerve paralyses with known origin imitate BP. Varicella-zoster virus (VZV), spirochete *Borrelia burgdorferi* and Hansen's *Mycobacterium leprae* undoubtly cause facial palsy. Poliotropic viruses (coxsackie, enteroviruses, etc.) attack directly facial nerve motor neurons. Autoimmune Guillain-Barré syndrome may also cause facial, often bilateral asymmetric palsy. Manifestations of Guillain-Barré syndrome have been repeatedly documented in patients with human immunodeficiency virus (HIV) infection. HIV infection can lead to reactivation of latent viral infections through immunity suppression. Sarcoidosis is another demonstrated cause of facial palsy. Isolated facial palsy can exceptionally be seen in vasculitic syndromes (affecting arterioles with diameter less than 100 mm), idiopathic intracranial hypertension, leukemias (nerve infiltration), hypothyroidism (myxedema), or tumors arising from facial nerve and its blood supply.

Case Report

J. P., a 21-year-old woman with a one-month history of left-sided suprachordal peripheral facial nerve paralysis of unknown origin, was admitted to the Department of Neurology in December 1999. On admission, severe grade paralysis, House Brackman scale (HBS) V-VI, was observed. The patient had previously been treated with oral prednisone and one local paramastoideal triamcinolone injection. Upon admission, oral prednisone was discontinued, and α-lipoic acid, pentoxifylline and B-group vitamins along with complex rehabilitation therapy were introduced. The patient's status started to ameliorate and three months of the onset of paralysis HBS grade IV was diagnosed.

The patient's personal history is very interesting, because it was the 11th BP episode from 1993. Her left facial nerve was affected eight times and the right one two times.

Table 1. Data on 11 Bell's palsy episodes in our patient

Year/month of onset	Possible cause*	Side	Therapy	Paralysis grade**	Outcome status***
1993 November	Gadfly bite	Right	Isoprinosine	4	1
1994 April	Viral infection	Left	Oral + local steroid, isoprinosine	4	1
1994 November		Right	Isoprinosine	3	1
1995 March	Cold exposure	Left	Local steroid, isoprinosine, acyclovir	4	1
1996 August	Cold exposure Gadfly bite	Left	Other****	3	1
1997 February		Left	Oral steroid, isoprinosine	4	1
1997 June	Stress	Left	Oral steroid	2	1
1998 May	Stress	Left	Oral steroid	2	1
1998 September		Left	Oral steroid	2	1
1999 June		Left	Oral steroid	2	1
1999 November	Gadfly bite	Left	Oral steroid	4	3

* patient's information;
** paralysis grade with use of modified HBS (1 – normal status, 2 – mild paralysis, 3 – moderate paralysis, 4 – severe paralysis);
*** paralysis grade before the onset of the next homolateral BP episode with use of modified HBS;
**** other therapy except for steroids and antiviral drugs

The first six BP episodes were treated at a hospital, and the next four episodes were treated on outpatient basis. All data on the 11 BP episodes are summarized in Table 1.

Repeat examinations with imaging techniques including temporal bone x-rays, skull and brain computed tomography (CT), and magnetic resonance imaging (MRI), showed normal findings. The last MRI was performed after the 11th BP episode. Clinical neurophysiology tests yielded the following results: visual evoked potentials (VEP), repetitive finding of chronic demyelinating optic tract damage; brainstem auditory evoked potentials (BAEP), repetitive normal finding; median nerve somatosensory evoked potentials (SSEP), normal finding; tibial nerve SSEP, normal finding; electromyography (EMG), focal or diffuse extracranial neuropathy exclusion, the affected facial nerve investigation repeatedly confirmed axonal damage type; electroencephalography (EEG), single recording of non-specific focal changes in the left temporal area with signs of brainstem structural dysfunction during hyperventilation. Cerebrospinal fluid (CSF) examination was performed twice and produced normal finding, including absence of antibodies against *Borrelia burgdorferi* (oligoclonal bands were not tested). The patient refused control CSF examination after the onset of the 11th BP episode. Repeat ophthalmologic examination including funduscopy did not produce any pathologic findings.

Otorhinolaryngologic examination was performed at all BP episodes with normal results including audiometry. The internal and pneumologic examinations showed physiologic findings (sarcoidosis was excluded). Focal infections and other pathologic conditions were ruled out by dental, urologic and gynecologic examinations. Serologic tests after the onset of the 1st – 6th episodes are summarized in Table 2 (performed at another hospital). We point out the fact that seropositivity for HSV-1 was never recorded.

The standard serologic test battery used at our department detected a significant level of antibodies against *Helicobacter (H.) pylori* one month after the onset of the 11th BP episode. Gastroduodenofibroscopy revealed the presence of *H. pylori* in the duodenal fluid. Therefore, our patient started standard antibiotic eradication therapy. Flow

Table 2. Serologic test results on 1st – 6th Bell's palsy episodes in our patient

Year – month of BP onset*	Serologic positivity for**
1993 – November (1st episode)	
1994 – April (2nd episode)	Leptospires
1994 – November (3rd episode)	
1995 – March (4th episode)	EBV, CMV
1996 – August (5th episode)	Parotitis
1997 – February (6th episode)	

* 7th –10th BP episodes were treated outpatiently without serologic testing;
** there are no data on antibody types and serologic methods used

Table 3. Results of serum testing for antineuronal antibodies

Type of antibody	IgM (ELISA)	IgG (ELISA)
Anti GM_1	Positive	Negative
Anti GD_{1b}	Negative	Negative
Anti GQ_{1b}	Negative	Negative
Anti sulfatide	Negative	Negative
Anti NSE*	Negative	Negative
Anti MAG**	Negative	Negative
Anti Hu	Negative	Negative

*antineuron specific enolase; **antimyelin associated glycoprotein

cytometry showed increased counts of lymphocytes, T cells, CD4+ (helper) cells, CD3+ (activated) cells, CD4+CD45RO+ (memory) cells, and B cells. Also, the blood level of circulating immune complexes was clearly elevated. Available serum antineuronal antibodies were tested and results are summarized in Table 3. Paraproteinemia was not detected and the remaining cellular and humoral immunity tests were within the physiologic range (phagocytic activity, acute phase proteins, immunoglobulins, complement proteins). Blood cell counting, biochemical serum analysis, and urine analysis were within the physiologic limits.

Discussion

The causes of BP episodes listed in Table 1 were considered as possible triggers. There were no conclusive facts to confirm the association of these events with subsequent onset of BP. The possible causes (triggering events) were: cold exposure, psychological and somatic stress, non-specified viral infections, and gadfly bites (there are more than 60 gadfly species in the Slovak Republic, and some of them may transmit several diseases). In four of eleven BPs, no potential cause (trigger factor) was identified.

It seems probable that different (often not identified) circumstances can lead to a cascade of processes that result in BP onset. At least the terminal part of the pathogenetic cascade is common to all BP cases, i.e. facial nerve edema in the fallopian canal with vasa nervorum compression. The severity and duration of compression result in different types of axonotmesis or prolonged neurapraxia. The grade of axonotmesis is decisive for the BP prognosis *quoad sanationem*.

Repeated BPs in our patient could be described as recurrent left and right facial nerve mononeuropathy (mononeuritis). Its inflammatory pathogenesis was very probable. Considering the fact that no common infectious agent for particular BP episodes could be determined as well as other results obtained, we suppose the recurrent BPs to have been the sequels of autoimmune attacks. The target of the immune system is an as yet unidentified antigen. All antineuronal antibodies tested were negative except for anti-GM_1 immunoglobulin M. Serum anti-GM_1 antibodies can be detected in patients with Guillain-Barré syndrome, multifocal motor neuropathy, amyotrophic lateral sclerosis, but also in some other neurologic diseases. The question is why there was no persistent positivity for anti-GM_1 immunoglobulin G after 11 BP episodes. It seems probable that the GM_1 neuronal antigen plays only a minor role in the pathogenesis of recurrent BP, and its positive serum testing in our case may have also been accidental. The suspected neuronal antigen relatively selective for the intracanalicular facial nerve segment still remains unrecognized. The autoaggressive reaction trigger factor may be a non-specific stimulus increasing the immune system activity (e.g., cold exposure, stress). Some antigen-defined stimuli (e.g., viral infection, gadfly bite) may also promote targeted or accidental activation of the autoaggressive lymphocyte selected clones. Some laboratory results appear to indirectly support these hypotheses (flow cytometry, immune complexes, *H. pylori* positivity, as this bacterium bears similar antigenic epitopes with peripheral nerves).

Taking the autoimmune process into consideration is interesting in view of the finding of bilateral demyelinating optic nerve damage (VEP). Despite normal CSF findings (although the presence of oligoclonal bands was not excluded), normal brain MRI, and normal clinical neurologic examination (except for the peripheral left facial nerve paralysis), it may have been a subclinical stage of a disease from the multiple sclerosis group.

After the last BP episode (the patient had been treated elsewhere before), we decided to treat her with long-standing non-specific immunomodulatory (immunosuppressive) enzyme therapy. We prescribed a drug containing several proteases, Wobenzym (Mucos Pharma, Germany) at a dose of 3x2 drg daily. This therapy was initiated in March 2000. Until this report, the patient did not have any new BP attack. The 30-month remission of recurrent facial nerve mononeuropathy (mononeuritis) is the longest disease-free period from the disease onset in 1993. Our hypotheses about the disease etiopathogenesis and the selected therapy efficacy will depend on the forthcoming patient's status evolution and on the results of laboratory tests in the future.

It should be emphasized that our patient had suffered 11 BP episodes (9 involving the left side and 2 involving the right side). According to literature data, the incidence of BP with 3 or more recurrences is 0.04% - 0.12%. There are no reports on more than 9 BP episodes in a single patient. Therefore, we conclude the presented case report is exceptional from this point of view. At the same time, we suggest that its pathogenesis may be closely related to the group of chronic autoimmune neurologic diseases with remitting-relapsing course (e.g., chronic inflammatory demyelinating polyneuropathy, multiple sclerosis).

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Sažetak

TESTIRANJE NA ANTINEURONSKA PROTUTIJELA U NEUOBIČAJENOM SLUČAJU PONOVLJENE BELLOVE PARALIZE

E. Kurča, Z. Kadaňka, M. Drobný, V. Nosál i M. Grofik

Pojam Bellove paralize (BP) danas označava perifernu paralizu ličnoga živca nejasne etiologije i patogeneze. BP nije stanje koje bi ugrozilo život bolesnika, ali može imati znatne estetske posljedice te izvazvati ozbiljne oftalomološke komplikacije (ulceracije rožnice). Ponovljene paralize javljaju se u 7% - 8% slučajeva BP. U literaturi je opisano samo dvoje bolesnika s četiri epizode BP od ukupno 1700 bolesnika, te samo jedan bolesnik s više od četiri epizode BP od ukupno 2414 slučajeva BP. U dostupnoj literaturi, najveći broj ponovljenih BP je devet. U radu se daje kratak pregled epidemiologije i etiopatogeneze BP, uz prikaz neuobičajenog slučaja ponovljene BP, uključujući raspravu o imunološkim patomehanizmima.

Ključne riječi: *Bellova paraliza – etiologija; Bellova paraliza – imunologija; Paraliza ličnoga živca - patogenost*