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CLINICAL CASE REPORT

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Facial Weakness, Otalgia, and Hemifacial Spasm: A Novel Neurological Syndrome in a Case-Series of 3 Patients With Rheumatic Disease

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Abstract: Bell palsy occurs in different rheumatic diseases, causes hemifacial weakness, and targets the motor branch of the 7th cranial nerve. Severe, persistent, and refractory otalgia having features of neuropathic pain (ie, burning and allodynic) does not characteristically occur with Bell palsy. Whereas aberrant regeneration of the 7th cranial nerve occurring after a Bell palsy may lead to a variety of clinical findings, hemifacial spasm only rarely occurs. We identified in 3 rheumatic disease patients (2 with Sjögren syndrome, 1 with rheumatoid arthritis) a previously unreported neurological syndrome of facial weakness, otalgia with neuropathic pain features, and hemifacial spasm.

We characterized symptoms, examination findings, and response to therapy. All 3 patients experienced vertigo, as well as severe otalgia which persisted after mild facial weakness had completely resolved within 1 to 4 weeks. The allodynic nature of otalgia was striking. Two patients were rendered homebound, as even the barest graze of outdoor breezes caused intolerable ear pain. Patients developed hemifacial spasm either at the time of or within 3 months of facial weakness. Two patients had a polyphasic course, with recurrent episodes of facial weakness and increased otalgia. In all cases, otalgia and hemifacial spasm were unresponsive to neuropathic pain regimens, but responded in 1 case to intravenous immunoglobulin therapy. No patients had vesicles or varicella zoster virus in spinal-fluid studies.

We have defined a novel neurological syndrome in 3 rheumatic disease patients, characterized by facial weakness, otalgia, and hemifacial spasm. As described in infectious disorders, the combination of otalgia, facial weakness, and 8th cranial nerve deficits suggests damage to the geniculate ganglia (ie, the sensory ganglia of the 7th cranial nerve), with contiguous involvement of other cranial nerves causing facial weakness and vertigo. However, the relapsing nature and association with hemifacial spasm constitute a unique part of this neurological syndrome.

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Abbreviations: IVIg = intravenous immunoglobulin, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, VAS = visual analogue scale, VZV = varicella zoster virus.

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INTRODUCTION

Bell palsy refers to a facial neuropathy which exclusively affects the motor branch of the 7th cranial nerve, causes hemifacial weakness,[1] and occurs in many rheumatic diseases. Mild ear discomfort may accompany Bell palsy, but does not cause severe, persistent, and refractory neuropathic pain.[1] There may be a range of clinical findings which reflects aberrant regeneration of the facial nerve after a Bell palsy. For example, facial synkinesis may cause involuntary contraction of the eyelid muscles, and can lead to squinting in response to voluntary movements such as smiling.[2] In contrast, hemifacial spasm (which causes involuntary and recurrent cocontraction of facial musculature)[3] is exceptionally infrequent compared with other regenerative findings. Therefore, hemifacial weakness, otalgia with neuropathic pain features, and hemifacial spasm have not been described as a clinical syndrome in any rheumatic diseases.

In this article, we for the first time describe such findings of hemifacial weakness, otalgia with neuropathic pain features, and hemifacial spasm occurring as a triad in rheumatic disease patients. There were several interesting and stereotypic findings. The severity of otalgia was striking. Even the barest graze of outdoor breezes caused excruciating allodynic pain and initially rendered the patients to be homebound. Other notable features that could be demonstrated in our rheumatic disease patients, and which are not characteristic of infectious disorders, included an intensely polyphasic course, and hemifacial spasm rapidly occurring after resolution of facial weakness. We consider how this rapid development of hemifacial spasm suggests mechanisms other than axonal regeneration. Further diagnostic, mechanistic, and therapeutic implications are discussed.

All patients provided informed consent.

Patient 1

A 32-year old, right-handed, Caucasian female with a history of seropositive Sjögren syndrome was referred for the evaluation of right-sided facial weakness, right-sided otalgia, and hemifacial spasm. One year prior to evaluation she developed right-sided facial weakness ascribed to a Bell palsy (see Timeline, Figure 1A). Evaluation revealed a ''lower-motor neuron'' pattern of facial weakness, with mild- and nonparalytic weakness involving forehead corrugation as well as other facial muscles. There were no vesicles noted in the right auditory canal. A lumbar puncture study was unremarkable, with no pleocytosis and normal total protein, and with no evidence of varicella zoster virus (VZV) or other viral infections as assessed by polymerase chain reaction (PCR) studies. Neuroimaging of the brain by magnetic resonance imaging (MRI) and magnetic resonance angiography studies was unremarkable. There were no other extraglandular manifestations.

Although attributed to a Bell palsy, our patient had additional symptoms which indicated damage to other cranial

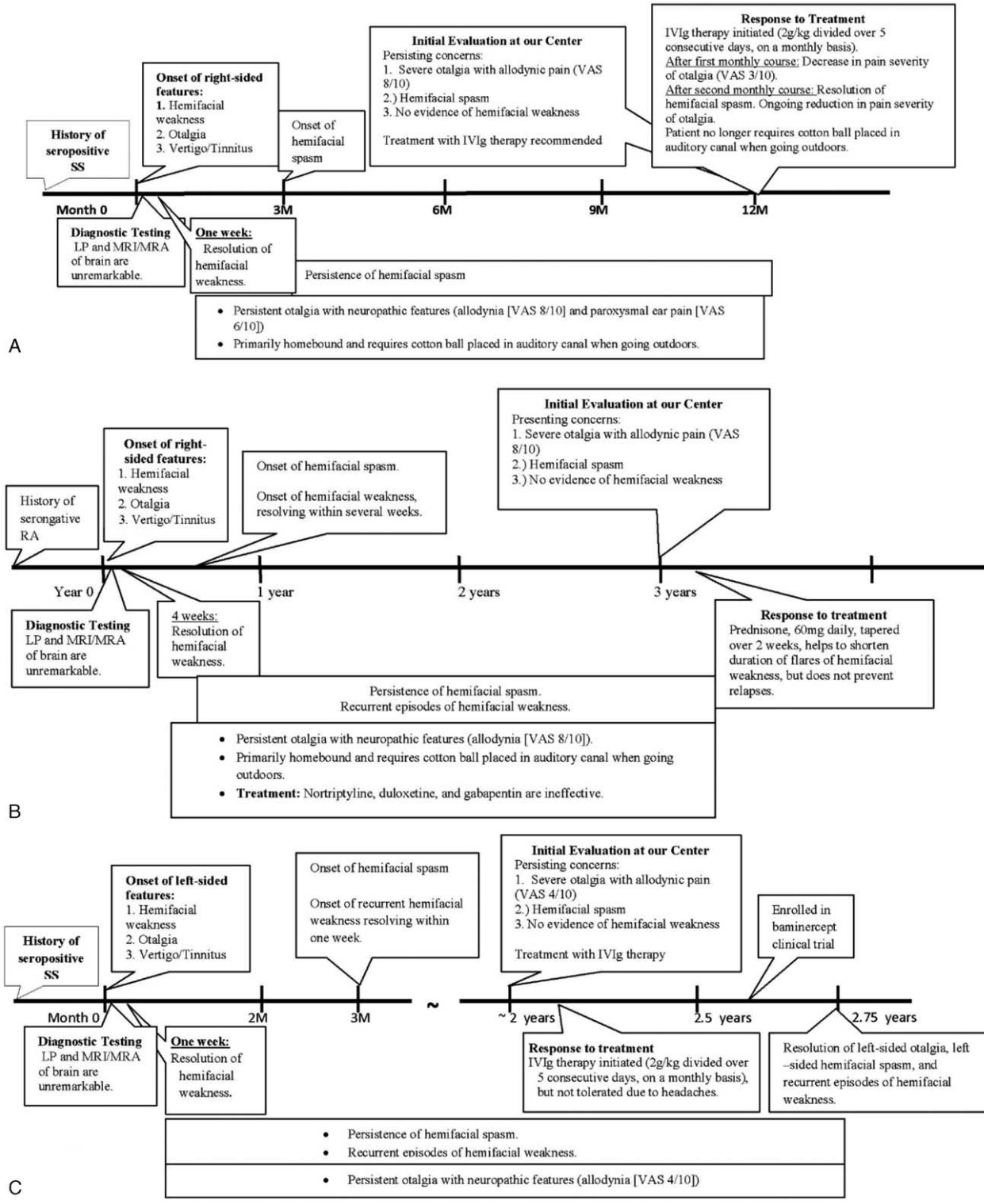

FIGURE 1. Timelines of patients' symptoms, examination findings, and response to treatment.

nerves and sensory ganglia, and therefore not consistent with a Bell palsy. For example, she experienced right-sided vertigo and tinnitus, indicating involvement of the 8th cranial nerve. However, the patient's most dramatic symptom was severe otalgia. She described persistent burning ear pain (graded as a 6/10 on a visual analogue scale [VAS]), as well as allodynic pain (graded as an 8/10 on a VAS). Such allodynic features were striking. Outdoor breezes triggered intolerable and excruciating

exacerbation of otalgia. In fact, the exacerbation of her otalgia by minimal, ambient breezes caused the patient to be primarily homebound. She was only able to go outdoors when she inserted a cotton ball inside her auditory canal. Treatment with oxcarbazepine 300 mg per-orally twice per day (PO bid) did not improve her pain, higher doses caused nausea, and the addition of even low doses of gabapentin at 100 mg per-orally 3 times per day (PO tid) caused severe fatigue.

Her otalgia and vertigo persisted even though her right-sided facial weakness had resolved within 1 week. Three months later she developed hemifacial spasm. There were involuntary episodes of right-sided eyelid closure, synchronously associated with grimacing-like movements and curling of her lips. She was referred for further evaluation.

Evaluation at our Center revealed an uncomfortable appearing female wearing a cotton ball inserted into her auditory canal and with hemifacial spasm. Cranial nerve examination revealed complete recovery of her right, lower-motor neuron facial palsy. Upon evaluation of the auditory canal, placement of an otoscope in her right-ear caused severe neuropathic pain. Such allodynic pain was also precipitated by lightly swabbing her ear with cotton. The remainder of her neurological examination was unremarkable.

In nonrheumatic disorders, damage to the geniculate ganglia may cause severe otalgia, with contiguous inflammation involving the motor branch of the facial nerve and the 8th cranial nerve resulting in facial weakness and vertigo.[4,5] Our patient had an identical constellation of symptoms (ie, otalgia, facial weakness, and vertigo), suggesting that her otalgia was mediated by damage to the geniculate ganglia. These findings are relevant given that our patient had Sjögren syndrome, in which neuropathic pain is associated with damage to the sensory ganglia of cranial nerves and the dorsal root ganglia[6,7] and can be selectively responsive to intravenous immunoglobulin (IVIg).[8–10] Therefore, treatment with IVIg was initiated. She received IVIg at a dose of 2 g/kg, administered over 5 consecutive days on a monthly basis. After a single course of IVIg, she reported a decrease in paroxysmal episodes of lancinating right-ear pain, now only experienced as a 3/10 on a VAS. After 2 doses of IVIg, she was able to remove the cotton ball from her ear, and allodynia due to outdoor breezes was now only experienced as a 2/10 on a VAS. There was also resolution of hemifacial spasm (see Timeline, Figure 1A). The patient has been maintained on monthly IVIg for 12 months with persistent efficacy in treating both burning and allodynic aspects of right ear neuropathic pain, and with resolution of hemifacial spasm (see section, ''Patient Perspectives,'' patient 1, at the end of article).

Patient 2

A 47-year old, right-handed, African-American female with a history of nonerosive, seronegative rheumatoid arthritis which was well-controlled on 15 milligrams (mg) of weekly methotrexate, was referred for the evaluation of right-sided facial weakness, right-sided otalgia, and ongoing hemifacial spasm. Three years prior to evaluation, she developed right-sided, lower-motor neuron facial weakness, which was mild and incomplete, ascribed to a Bell palsy, and resolved within 4 weeks. However, she also experienced right-sided tinnitus, vertigo, and otalgia associated with severe allodynic pain (see Timeline, Figure 1B). Similar to patient 1, she also reported that outdoor breezes caused severe exacerbation of her otalgia. Also similar to patient 1 she was unable to exit her home without placing a cotton ball into her auditory canal. Evaluation revealed no vesicles in her right auditory canal. Lumbar puncture studies were unremarkable, with no pleocytosis and normal total protein, and with no evidence of VZV or other viral infections as assessed by PCR studies. Neuroimaging of the brain by MRI and magnetic resonance angiography studies was unremarkable. After 4 weeks, she had complete resolution of facial weakness. However, she had persistent vertigo and otalgia, described as an 8/10 on a VAS. Polysymptomatic therapies that led to intolerable side effects or which were ineffective included topiramate 50 mg PO bid (discontinued because of cognitive impairment), nortriptyline 100 mg PO each bedtime (discontinued because of transaminitis), duloxetine 60 mg PO once-per day (qd), and gabapentin 300 mg PO tid.

Within months, she subsequently developed a polyphasic disease course. She developed recurrent episodes of right-sided facial weakness which resolved within 2 to 3 weeks, and was associated with increased otalgia (ie, described as a 10/10 on a VAS). During the second episode, she developed right-sided hemifacial spasm at the same time as the onset of facial weakness. Episodes of hemifacial spasm persisted after resolution of hemifacial weakness. She was hospitalized during these first 2 flares for concern about cerebrovascular disease, but MRI of the brain revealed no evidence of a cerebrovascular event. Her polyphasic course of recurrent hemifacial weakness continued unabated, with 4 recurrent episodes occurring in the 5 months before evaluation at our Center.

Evaluation at our Center revealed an uncomfortable appearing female wearing a cotton ball inserted into her auditory canal and with hemifacial spasm. There was otherwise complete recovery of facial weakness. Her insurance company did not approve treatment with IVIg. Treatment with prednisone at 60 mg PO qd (tapered over 2 weeks) has not prevented relapses and has only led to more rapid resolution of recurrent facial weakness during disease flares. She has continued to have hemifacial spasm, as well as otalgia which has been persistent, severe, and unresponsive to corticosteroids (see section, ''Patient Perspectives,'' patient 2). Her rheumatoid arthritis has been in remission on methotrexate, and she did not wish to try additional immunosuppressive therapy (see Timeline, Figure 1B).

Patient 3

A 40-year old, right-handed, Caucasian female with seropositive Sjögren syndrome and without other extraglandular manifestations was referred for the evaluation of recurrent episodes of left-sided otalgia, facial weakness, and hemifacial spasm. Two years prior to evaluation, she developed left-sided, lower-motor neuron facial weakness, which was incomplete, ascribed to a Bell palsy, and resolved within 1 week. However, she also experienced left-sided otalgia, sensitivity to noise, vertigo, and tinnitus. Lumbar puncture studies revealed no evidence of VZV or viral infections as assessed by PCR studies. Neuroimaging of the brain by MRI revealed only nonspecific white matter disease. Similar to patient 1 and patient 2, her otalgia persisted even after resolution of hemifacial weakness. Evaluation revealed no vesicles in her left auditory canal. She had persistent allodynic pain of her left ear, described as a 4/10 on a VAS, but she did not wish to start any neuropathic pain medications.

Three months later, she developed left-sided hemifacial spasm and acutely worsening otalgia. Similar to patient 2, she subsequently developed a polyphasic disease course. She

developed recurrent episodes of left-sided facial weakness which resolved within 2 days to 1 week, and was associated with increased otalgia (ie, described as an 8/10 on a VAS). Altogether, she experienced 6 recurrent episodes prior to evaluation at our Center.

Such symptoms and neurological findings prompted evaluation at our Clinic. She was noticed to have complete recovery of left-sided facial weakness but with persistent episodes of hemifacial spasm. Lightly stroking her ear with a cotton swab caused allodynic pain. Treatment with 2 g/kg of IVIg was started but needed to be terminated after the first month due to intolerable headaches. She has since been enrolled in a double-blinded, placebo-controlled, clinical trial assessing the efficacy of baminercept in Sjögren syndrome. Although it is currently not known whether she has received the clinical drug or the placebo, there was complete amelioration of otalgia and episodes of left-sided hemifacial spasm within 2 months (see Timeline, Figure 1C).

RESULTS

Clinical Findings, Diagnostic Assessment, Therapeutic Interventions, and Outcomes

The clinical features of the 3 patients are summarized in Table 1. All patients experienced mild, lower-motor neuron facial weakness, which resolved within 1 week (patients 1 and 3) and within 4 weeks (patient 2). In addition, all patients had severe otalgia at the outset of facial weakness, and which persisted with unrelenting pain intensity even after facial weakness had resolved. The quality of the ear pain had neuropathic features and was associated with burning and allodynic pain. As noted in the vignettes, patients 1 and 2 were virtually homebound, as even minimal outdoor breezes could precipitate excruciating, allodynic pain. In addition, both the unprovoked and allodynic features of otalgia were refractory to polysymptomatic therapies typically used for neuropathic pain. All 3 patients had involvement of the 8th cranial nerve, experiencing vertigo and/or tinnitus. Interestingly, patients 2 and 3 were able to distinctly articulate disease ''flares,'' in which there was recurrent facial weakness and episodically worsening otalgia. All patients developed episodes of hemifacial spasm. Whereas hemifacial spasm can occur during recovery from severe and even hemiparalytic injury,[3] all of our patients only had mild, brief, and complete resolution of facial weakness. Furthermore, whereas there may be a prolonged interval between hemifacial spasm and the onset of hemifacial weakness,[3] patient 2 developed hemifacial spasm at the same time as the onset of facial weakness. Patients 1 and 3 developed hemifacial spasm only 3 months after hemifacial weakness had completely resolved.

Patient 1 had a dramatic and complete response to IVIg, with striking diminution of otalgia and elimination of hemifacial spasm. Patient 3 was enrolled in a clinical trial assessing the efficacy of baminercept in Sjögren syndrome, and although it is unsure whether she received the placebo or the study drug, she similarly to patient 1 had significant improvement in otalgia and resolution of hemifacial spasm (see section, ''Patient Perspectives,'' patient 3).

DISCUSSION

We here describe a novel neurological syndrome in 3 rheumatoid arthritis patients, defined by a clinical trial of

TABLE 1. Clinical Features of the Syndrome of Facial Weakness, Otalgia, and Hemifacial Spasm

Clinical Features and Ancillary Investigations	Patient 1	Patient 2	Patient 3
Rheumatic disease	Sjögren syndrome	Rheumatoid arthritis	Sjögren syndrome
Lower-motor neuron, hemifacial weakness	Yes	Yes	Yes
Mild weakness without paralytic features at clinical nadir	Yes	Yes	Yes
Resolution of facial weakness within days to weeks	Yes, within 1 week	Yes, within 4 weeks	Yes, within 1 week
Presence of otalgia ipsilateral to facial weakness	Yes	Yes	Yes
Persistence of allodynia after resolution of facial weakness	Yes	Yes	Yes
Patients rendered home-bound without placement of cotton in auditory canal	Yes	Yes	No
Clinical improvement of otalgia in response to polysymptomatic treatment	No	No	Patient refused neuropathic pain medicines
Clinical improvement of otalgia in response to Immunomodulatory therapy	Yes, with IVIg	No response to ongoing methotrexate therapy prescribed for RA	Questionable, enrolled in clinical trial, unsure if patient received study drug or placebo
Involvement of 8th cranial nerve	Yes, vertigo and tinnitus	Yes, vertigo and tinnitus	Yes, vertigo
Polyphasic course	No	Yes	Yes
Presence of hemifacial spasm	Yes	Yes	Yes
Interval between facial weakness and onset of hemifacial spasm	Three months	Concomitant onset of hemifacial spasm with hemifacial weakness	Three months

IVIg = intravenous immunoglobulin.

hemifacial weakness, otalgia presenting with severe neuropathic pain, and hemifacial spasm. Although the combination of hemifacial weakness with otalgia and painful facial neuropathies may occur in infectious disorders (see below), the invariable emergence of hemifacial spasm is unique to our patients. Other notable and unique features included a relapsing course in 2 patients, severe otalgia which persisted after facial weakness had extinguished, and hemifacial spasm which presented even when there had been no clinical indicators of severe axonal injury (ie, absence of severe facial weakness). We below consider how the integration of these symptoms with findings on the neurological examination offers valuable insight into mechanisms which have therapeutic implications.

The characteristics of our patients' otalgia were striking. As noted in the case vignettes, patients 1 and 2 had persistent otalgia and were reluctant to leave their homes, as even the barest graze of ambient wind caused intolerable, allodynic pain. Both patients had independently settled on strategies of constantly wearing cotton balls in their ear to mitigate such neuropathic pain. In addition to such allodynic pain, all patients also had spontaneous neuropathic pain, which was described as being paroxysmal and burning. Although mild ear discomfort may accompany facial weakness in Bell palsy,[1] otalgia which is severe, persists after resolution of facial weakness, and experienced as neuropathic pain does not characteristically occur. The severity of such neuropathic pain could be refractory to such polysymptomatic approaches. The persistence of such otalgia therefore suggests mechanisms which do not exclusively target the motor branch of the facial nerve.

Furthermore, all of our patients had hemifacial spasm. The nature and temporal relationship of hemifacial spasm associated with facial weakness is instructive, as this supports mechanisms other than axonal damage. Hemifacial spasm may occur months to years after severe facial weakness and can reflect a slow and dysregulated regenerative response after significant axonal injury.[3] In contrast, hemifacial spasm in our patients occurred in the context of mild and quickly resolving facial weakness, which indicates that there was no significant axonal injury. This suggests that the development of hemifacial spasm in our patients, which could temporally present close to onset of facial weakness, was not due to dysregulated axonal regeneration. Interestingly, there are several immune-mediated pain disorders in which neuronal hyperexcitability is the mechanism underscoring abnormal movements such as muscle rippling, dystonia, and cramping.[11] Similar to our patients, it was suggested that such disorders may represent mechanisms of neuronal hyperexcitability as opposed to axonal regeneration, and may potentially occur at the level of ganglionic structures.[12]

The association of facial weakness with otalgia and other facial pain disorders has been established for Ramsay-Hunt disorder, which was first described by James Ramsay Hunt in 1905.[4,5] This syndrome is characterized by severe otalgia, facial weakness, and vestibulocochlear dysfunction (ie, diminished hearing, tinnitus, or vertigo). Reactivation of the VZV in the geniculate ganglia causes severe otalgia. In addition, facial weakness and vertigo occurs due to contiguous inflammation affecting the motor branch of the cranial nerve and the 8th cranial nerve. Similarly, our patients shared overlapping features with Ramsay-Hunt syndrome, including facial weakness, otalgia, and vertigo. This shared constellation of symptoms with Ramsay-Hunt disorder further supports that our patients also had otalgia with severe neuropathic pain due to immune-mediated mechanisms which target the geniculate ganglia.

However, it is important to emphasize discriminating findings seen in our patients versus this traditional Ramsay-Hunt disorder. First, none of our patients presented with a vesicular rash, or with evidence of VZV viral PCR on cerebrospinal fluid studies. Secondly, there were additional features suggesting that our patients did not constitute a forme fruste of the Ramsay-Hunt syndrome (ie, zoster-sine-zoster), in which the neurological features of Ramsay-Hunt syndrome may occur without detectable, vesicular eruptions. Two patients experienced recurrent attacks of hemifacial weakness and hemifacial spasm. Such a polyphasic course is not usually seen as a part of infectious Ramsay-Hunt syndrome, in which deficits are usually monophasic and not relapsing.

It is intriguing how patient 1 had near-eradication of paroxysmal and allodynic aspects of her neuropathic pain with IVIg immunomodulatory therapy. Within 2 months of IVIg therapy, she was again able to walk outside without the protection of a cotton ball placed in her ear, was able to discontinue all other neuropathic pain agents, and with the intensity of neuropathic pain decreasing from a 10/10 to a 2/10 on a VAS. In patients with Sjögren syndrome, IVIg has been shown to be effective in treating other neuropathic pain disorders which target the dorsal root ganglia and the sensory ganglia of cranial nerves[8–10] even when such neuropathic pain is refractory to polysymptomatic approaches and potent immunosuppressive therapy (ie, cyclophosphamide). Therefore, the selective efficacy of IVIg in patient 1 similarly supports that our patient had otalgia mediated by mechanisms targeting the sensory ganglia of cranial nerves. We were not able to secure insurance approval to provide IVIg treatment in patient 2, and patient 3 was not able to tolerate IVIg therapy. However, patient 3 similarly had improvement of otalgia and resolution of hemifacial spasm in the context of a clinical trial. We are currently awaiting the unblinding phase to determine whether patient 3 was indeed assigned to the baminercept arm of this study. Nevertheless, subsequent analysis has noted that patient 3 has had a durable increase in her unstimulated salivary flow, which further supports assignment to the treatment as opposed to the placebo arm.

In summary, we report on a new, previously unrecognized neurological disorder in rheumatic disease patients, characterized by facial weakness, otalgia with neuropathic features, hemifacial spasm, and with both otalgia and hemifacial spasm persisting after the extinction of mild facial weakness. Our findings suggest that rheumatic disease patients with presumptive Bell palsy should be queried about the concomitant presence of otalgia, and monitored for the presence of hemifacial spasm. Further studies in rheumatic disease cohorts can now assess for frequency, etiopathogenesis, and treatment for the constellation of these findings.

PATIENT PERSPECTIVES

Patient 1: ''IVIg has worked wonders. After the first week of infusions, my symptoms started to improve and continued to do so with monthly infusions. It was a joy to be able to start to do small things again such as being able to consistently open my eyes, not having them shut due to spasms, and not to have ear pain every day. I could leave my apartment and walk outside without assistance and without cotton in my ears. There were days, and eventually weeks, where I did not have any nerve symptoms. It sounds like a miracle, but it was not.''

Patient 2: ''See the way you're looking at me now, the way I have this cotton ball in my ear? It's 10 degrees outside, and I don't want any wind touching my ear. The ear pain feels like I

have someone drilling in my ear. You know when you have a cavity and they're drilling without novocaine? It's that same type of drilling pain in your ear. Any type of wind or air can set this drilling off. Right after the ear hurts, it sets off the spasms in my face. Sometimes when I'm outdoors and shopping, and someone looks at my face spasms they think I'm having a stroke because my face kind of slides. I've had managers at pharmacies who insisted on calling ambulances because they see the spasms. I tell them I'm not having a stroke, but they look at me and tell me, 'Yes, you are.' In the beginning, the ambulances insisted on taking me, before I knew my own body and know that my spasm is not a stroke. I just know my own body.''

Patient 3: ''Prior to the study drug, the facial spasms were so awful and often that I didn't want to go out of the house. First of all, I was embarrassed to see anyone looking at me. There was this constant pulling on your face, like when you're in the cabin pressure of an airplane with the airplane taking off. It never stopped, and I just wanted to lay down. I completely withdrew from friends and just stayed in the house. It got so bad that I didn't feel comfortable going to work, because I was working with customer service in the retail business, and I didn't feel comfortable interacting with my face pulling to the side. After the study drug, I just didn't have the spasms anymore. I felt like I could go out and about, and I wasn't embarrassed to go out anymore. I felt comfortable going back to work, being with friends, and just glad again to have a normal life.''

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