SHORT REPORT

Sympathetic contralateral vestibulopathy after unilateral zoster oticus

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Abstract
A unique case of initially right sided varicella zoster induced Ramsay-Hunt syndrome with complete vestibular loss is reported. The patient subsequently developed deficits of the left vestibule 5 months later. An autoimmune pathogenesis of the left vestibular failure rather than bilateral varicella zoster infection was suggested by the following data: (1) no evidence of vesicular eruptions on the left auricle and the virtual absence of antiviral antibodies after onset of bilateral vestibulopathy; (2) prompt response of the left vestibule to immunosuppressive therapy with corticosteroids; and (3) presence of atypical nervous tissue specific autoantibodies against a 45 kDa protein.

Patient and methods
PATIENT
Ramsay-Hunt syndrome on the right side
A 43 year old woman was admitted with peripheral facial nerve palsy, rotational vertigo, and hearing loss due to herpes zoster neuritis of the right VIIth and VIIIth cranial nerves. Neuro-ophthalmologic examination showed a horizontal-rotatory spontaneous nystagmus (fast phase) beating to the left ear and a complete ocular tilt reaction to the right, a pattern of head tilt, skew deviation, ocular torsion, and tilt of perceived vertical caused by a combined lesion of the superior and inferior branches of the vestibular nerve. Polymerase chain reaction (PCR) demonstrated varicella zoster virus (VZV)-specific DNA in the CSF and serological tests for antiviral antibodies in CSF were positive (IgM titre 1:160, IgG 220 units/ml as determined with the Enzygnost anti-VZV/IgG kit from Behring, Germany). Further details on the same patient are available.

Stable condition after antiviral therapy
The patient was treated with intravenous acyclovir for 14 days. Three months after symptom onset, there was no spontaneous nystagmus and no detectable ocular tilt reaction. Unsteadiness of gait had also disappeared. Only mild oscillopsia could still be triggered by fast head movements toward the right. At that time, rotatory and caloric testing of the horizontal semicircular canals (hSCCs) by electronystagmography disclosed complete loss of right peripheral vestibular function, whereas excitability of the left labyrinth was normal (fig 1). Pure tone audiograms showed normal hearing in the left ear and anacusis in the right ear. Palsy of the right facial nerve persisted.

Onset of left vestibular dysfunction
Five months later, the patient complained of tinnitus in the left ear and a slowly increasing unsteadiness of gait, particularly in the dark or accompanying rapid head movements. Sudden passively induced head rotations to both sides (Halmagyi-Curthoys test) elicited pathologic saccades indicating a bilateral deficit of the horizontal vestibulo-ocular reflex. Electronystagmography at that time disclosed complete caloric unresponsiveness of the right and left hSCCs (fig 1A), and no postrotatory
nystagmus could be elicited (fig 1B), indicating bilateral vestibulopathy. A pure tone audiogram of the left ear was within the normal range at all frequencies tested, and there was no facial palsy on the left side.

The absence of vesicular eruptions in or around the left ear canal and the results of CSF examinations gave no evidence of viral reactivation. Particularly, anti-VZV IgM was no longer detectable, anti-VZV IgG had fallen to 0.023 units/ml, and PCR for VZV-specific DNA was negative. As an autoimmune process was assumed to affect the left vestibulocochlear nerve, corticosteroid treatment (1 g/day methylprednisolone for 5 days, slowly tapering to 10 mg/day) was immediately initiated. Within 2 days tinnitus disappeared and gait disturbances improved appreciably. Caloric (fig 1A) and postrotatory nystagmus to the left (maximum slow phase velocity of postrotatory nystagmus 22 °/s, time constant 25s; fig 1B) reappeared, indicating recovery of left labyrinth function.

METHODS

Electronystagmography
Caloric and rotational tests of horizontal semicircular canal function were performed using direct current electro-oculography (EOG) in complete darkness to exclude visual fixation.

**Figure 1** Electronystagmographic recordings. (A) Caloric nystagmus (44°C), left ear. Upper curve: 2 weeks after onset of zoster oticus on the right side; maximum slow phase velocity of the caloric nystagmus was 16 °/s. Middle curve: the left hSCC became virtually unresponsive to caloric stimulation indicating contralateral vestibulopathy. Lower curve: after immunosuppressive therapy, function of the left labyrinth recovered. (B) Rotational testing (90 °/s to the right) for left labyrinth function in complete darkness; postrotatory nystagmus. Stop designates the abrupt halt of the rotatory chair. Upper curve: 2 weeks after onset of zoster oticus on the right side, rotation to the right elicited a normal postrotatory response of the left labyrinth (maximum slow phase velocity 22 °/s). Middle curve: 5 months later, absence of postrotatory nystagmus indicates contralateral vestibulopathy. Lower curve: after immunosuppressive therapy, rotation to the right elicited a postrotatory nystagmus to the left (maximum slow phase velocity 22 °/s), indicating recovery of the left labyrinth. Caloric irrigation and rotational testing of the right labyrinth disclosed complete and persistent loss of vestibular function (not shown).

**Immunofluorescence**
Cryosections of rat membranous labyrinth (ampulla, SCC, and utricle), cochlea, cerebellum, brain, and kidney were analysed for serum antibody binding as described elsewhere in detail.5

**Western blot**
Rat organs (nerve containing ganglia, cerebellum, brain, liver, kidney, spleen, lung, and eye) were homogenised in a buffer containing 5%
The most common ANA species (SS-A, SS-B, U1-RNP associated antigens, Sm-antigen, Scl-70, and Jo-1) were not detectable by specific immunodiffusion. According to the immunofluorescence (IF) data, nervous tissue specific and non-specific ANAs are superimposed on cerebellar sections. In an attempt to characterise the anticerbellar antibodies in more detail, western blots for anti-Hu,9 anti-Yo,10 11 and anti-Ri12 were performed, but they did not detect these specificities at a serum dilution of 1:250.

WESTERN BLOTS USING DIFFERENT RAT ORGANS
Because immunofluorescence assays and western blots did not yield evidence of well characterised antineuronal antibodies, we screened the patient’s serum for a large panel of antibody specificities, using western blots from eight different rat organs (nerve, cerebellum, brain, liver, kidney, spleen, lung, and eye). Serum was obtained at the onset of left vestibular failure and 2 months later—that is, after high dose corticosteroid treatment. The patient’s serum IgG (diluted 1:250) produced a prominent, broad antigen band of 45 kDa in cerebellum and brain and a weak band in nerve. No antibody binding to liver, kidney, spleen, lung, or eye was found (fig 2 C). Two months later, the amount of nervous tissue specific IgG was strongly reduced (fig 2 C).

Discussion
POSSIBLE AUTOIMMUNE AETIOLOGY OF LEFT VESTIBULAR DYSFUNCTION
Failure of the left hSCC 5 months after complete loss of right vestibular function due to herpes zoster oticus could result from a contralateral reactivation of the virus or from autoimmune attack on the left vestibule. In this patient, an immune aetiology seems much more likely, because vesicular eruptions in the left ear were absent and anti-VZV antibodies had dropped to very low concentrations. As in autoimmune sensorineural hearing loss (SNHL),13 the onset of symptoms in the left labyrinth was sudden and the course rapidly progressive. Interestingly, hearing and facial nerve function remained intact on the left side. The appearance of nervous tissue specific antibodies in the patient’s serum during the acute phase and the prompt improvement of vestibulocochlear symptoms on the left side after corticosteroid treatment also suggested an autoimmune process.

The association of infection with viruses of the herpes family and autoimmune disorders is well known—for example, in herpes ophthalmicus,14 stromal keratitis,15 and Guillaum-Barré syndrome.16 Marek’s disease in the chicken is considered an animal model of virally induced autoimmune demyelination of peripheral nerves.17 The pathology of viral vestibular neuritis shows destruction of vestibular branches of the VIIIth cranial nerve.18 Immunofluorescence assays and western blots with the serum of our patient also suggested a specific autoimmune process against membranous labyrinth and neuronal structures. There was detectable humoral reactivity against inner ear
organs and a specific humoral response was mounted against nervous tissue. The structural basis of virus induced autoimmune processes may be a sequence homology between viral and host proteins (molecular mimicry), as exemplified by a 12 amino acid sequence found in the glycoprotein D of VZV and in the peripheral myelin protein P0. Alternatively, the inflammatory reaction may expose antigens normally sequestered from the immune system. Because T cells reactive to highly tissue specific antigens escape from clonal deletion in the thymus, they may gain access to their antigen and be activated locally during an ongoing antiviral immune response.

AUTOANTIBODIES AGAINST NERVOUS TISSUE-SPECIFIC 45 KD PROTEIN

The high titre of antinervous tissue antibodies and the relatively low titre of antilabyrinthine antibodies seems to be inconsistent with a sympathetic aetiology of contralateral vestibulopathy in this case. The autoantibody concentrations and the results of clinical evaluation do not correlate. Likewise, the concentration of antilabyrinthine antibodies in patients with bilateral vestibulopathy does not correlate with the severity of the dysfunction. Also, other autoantibody species associated with certain forms of hearing loss are rather markers than essentials of an assumed autoimmune process.

Figure 2  Characterisation of the patient’s autoantibodies. (A) Immunofluorescent labelling of a cryosection of rat cerebellum by serum IgG (diluted 1:100) from our patient. Note the exclusively nuclear staining. (B) and (C) western blot of different rat organs developed with the patient’s serum (1:250) obtained on admission (B) and 2 months later (C). Lanes: N=nerve; C=cerebellum; B=brain; L=liver; K=kidney; S=spleen; Lu=lung; E=eye. The size of marker proteins is given in kDa. (B) A prominent antigen of 45 kDa is labelled in cerebellum and brain. (C) Two months later, labelling is clearly reduced.
Because the neurological examination did not disclose any signs other than the aud iovestibular deficits, we consider that these autoantibodies are non-pathogenic. If the antibodies against nervous tissue detected in this study were pathogenic agents, they should have caused more general signs, particularly cerebellar ones.

Autoimmune damage to cochlear structures in rapidly progressive SNHL is often associated with an IgG response to a 68 kDa protein, which was identified as heat shock protein 70 (hsp 70). Another dominant humoral autoantigen in SNHL is the peripheral myelin P0, which has a molecular weight of 30 kDa. Because the expression of both hsp 70 and P0 lacks organ specificity, these autoantibodies are probably not the pathogenic agents in SNHL. Our patient’s serum reacted neither with a 68 kDa nor with a 30 kDa protein, but rather with a CNS related 45 kDa antigen.

This seems to be the first reported case of sympathetic vestibular failure on the basis of: (1) sequential BV with a rapidly progressive course; (2) response to immediate immunosuppressive therapy before the damage has become irreversible; (3) exclusion of other aetiologies except an immune mediated process; (2) response to immediate immunosuppressive therapy before the damage has become irreversible; (3) exclusion of other aetiologies except an immune mediated process; (4) exclusion of other aetiologies except an immune mediated process; and hearing remained even intact in the left ear. The autoimmune reaction was highly specific. We think that a cellular immune process against the vestibular nerve (1) caused the left vestibular failure, and (2) triggered the synthesis of the autoantibodies against a 45 kDa nervous tissue-specific protein.

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