octapeptide coding repeats in the PRNP gene. *Proc Natl Acad Sci USA* 1991;**88**:10926–30.

- 4 Croes EA, Theuns J, Houwing-Duistermaat JJ, et al. Octapeptide repeat insertions in the prion protein gene and early onset dementia. *J Neurol Neurosurg Psychiatry* 2004;**75**:1166–70.

A case of idiopathic musical hallucination with increasing repertoire

A musical hallucination is defined as a type of auditory hallucination characterised by the perception of music without an external source.¹ Reports in the literature state that musical hallucinations are common in women, and are associated with ageing, deafness,^{2,3} brain diseases (epilepsy, tumour, stroke, meningitis and neurosyphilis),^{3,4} psychiatric diseases (schizophrenia and manic depression),^{3,4} toxic states (alcohol)² and drugs (antidepressants,¹ salicylate,⁵ quinine and aspirin⁴). Some authors proposed that, when listening to music, the auditory input is processed by three stages, operating in a hierarchical fashion: perception of individual sounds, perception or imagery of pattern in segmented sound, and encoding or recognition of patterned segmented sound.⁶ It is supposed that musical hallucinations are caused by abnormal autonomous activity in the auditory brain systems responsible for normal musical imagery.⁷ It seems reasonable to say that, in acquired peripheral deafness, there is impoverished auditory input that allows spontaneous activity between perception or imagery and encoding or recognition of pattern in segmented sound.⁶ Regarding lesions in the central nervous system, these lesions may alter the threshold of spontaneous activity within the network for the perception and imagery of music.⁶ We describe a patient with musical hallucination who experienced an increase in the repertoire of musical hallucinations as she sang various songs, and discuss some of the undetermined problems related to cognitive processing of music: melody, accompaniment and timbre.

In July 2002, a 75-year-old, right-handed woman was visiting a hospital on a daily basis to see her husband who had been admitted for cerebrovascular disease. At 17:00 h each evening, a famous Japanese nursery song, "A red sunset," was heard from the neighbouring town office. The music was sung by a chorus of children and accompanied by an orchestra. On the evening of 4 August 2002, the woman suddenly heard the song, "A red sunset," while in the kitchen of her home. She immediately realised that this was not a true phenomenon, as it was not 17:00 h and her home was some distance from the hospital. The melody of the hallucinated song was the same as that of the original music she had heard in the hospital, but there was no orchestral accompaniment. The musical hallucination was not lateralised to either ear or side of space. Previous to this, the woman had not experienced any hearing deficits, visual or tactile hallucinations, perceptual disturbances, gait or balance disturbance, or dementia. After the initial hallucination, she continued to hear the song, which repeated constantly. In addition, the volume of the song was increased when she was in noisy surroundings. The musical hallucination went away only when the woman spoke, sang or listened to music. To stop the musical hallucination, she resorted to singing various songs.

These songs, which had no personal significance to her, then became incorporated in her musical hallucination. As a result, all the songs in her musical hallucination, including "A red sunset," would sound in the order. The woman would hear the hallucinated songs with text and accompaniment by the "ohayashi," which is a traditional Japanese vocal accompaniment consisting of short, untuned voices. By this time, the timbre of "A red sunset" in her musical hallucination had changed from the chorus of children to her own voice. The timbre of the other hallucinated songs was either that of her own voice or of a famous singer that she had often listened to on the radio or television. The tempo of each song would gradually increase, and then the next song in the succession was heard. There was no musical hallucination of new songs sung by others, or related to persistent perception of non-musical sounds.

In September 2002, the woman was admitted to our hospital. She was fully conscious, and attained a full score on the Mini-Mental State Examination (30/30), and normal scores on a Japanese version of the Wechsler Adult Intelligence Scale—Revised (WAIS-R; verbal IQ 91, performance IQ 95, total IQ 92). She clearly remembered daily and social events. The Japanese version of the Wechsler Memory Scale—Revised (WMS-R) yielded a normal score for General Memory Index and Concentration of 99 and Attention Index of 99. The woman did not have any weakness in her limbs, and was not experiencing any sensory disturbances, aphasia, dyscalculia or difficulties in visual discrimination. Her hearing was unimpaired, and pure tone audiometry was normal. Auditory brain stem responses failed to delineate a brain stem dysfunction. The electroencephalogram showed normal background activity and no epileptic discharge. Magnetic resonance imaging and magnetic resonance angiography of the brain showed no abnormal findings. ¹²³I-Isopropyl amphetamine single-photon emission computed tomography did not show any defects or abnormal accumulation of isotopes. Her laboratory investigation was unremarkable. There were no abnormal findings in her cerebrospinal fluid, and a *Treponema pallidum* haemagglutination assay was negative. She had no arrhythmia and no other risk factors for cerebrovascular events. She received a normal score on the Hamilton Depression Scale, and consultation with a psychiatric specialist ruled out any psychogenic diseases. Before the onset of the musical hallucination, she received no drugs. She was treated by carbamazepine, diazepam and antidepressants in vain for 6 months, and the drugs were stopped. A year after the onset, the woman's musical hallucinations had gradually improved. The volume had decreased, and she was able to experience short periods of silence. By September 2004, she was experiencing musical hallucinations for only half a day at a time.

Our patient was an elderly woman who was congruent with risk factors of musical hallucination,² but had no apparent hearing loss, organic lesion, or other causes, so we diagnosed her with idiopathic musical hallucination. The characteristics of this case are as follows:

- musical hallucination of "A red sunset" in which the melody contained portions of real music, but the orchestral accompaniment was omitted;

- accompaniment consisting of ohayashi, which the woman had never listened to, in combination with the hallucinated songs;
- the timbre of the musical hallucination was either the voice of the patient or of a famous singer;
- the repertoire of hallucinated songs increased as the patient sang various songs.

Studies on human functional imaging and lesions indicate that musical perceptual sub-components (such as melody and timbre) are likely to have distinct anatomical substrates distributed in a network of cortical areas centred on the superior temporal lobe beyond the primary auditory cortex.^{3,7,8} Therefore, it seems reasonable to suppose that these sub-components could be differentially affected by the pathophysiological process causing musical hallucination.^{3,7-9} From these findings, it is possible to construct two hypotheses:

- accompaniment and timbre may be independent components of musical perception in which information is stored independently in the brain, retrieved from the memory and combined with a frequently sung melody. It was supposed that the melodic component of the musical piece has the strongest representation, whereas other elements, such as orchestration and background ohayashi, are secondary, and could be eliminated in hallucinatory form;
- the number of hallucinated songs our patient experienced increased as she sang various songs, and disappeared when she listened to real music. We surmise that when the patient sang, the abnormal activity of neurones concerned with perception and imagery of music was suppressed by the actual auditory input. Persistent abnormal firing patterns of neural circuits in the absence of such external stimulation may have increased the repertoire of musical hallucinations by incorporating reactivated musical memories into the abnormal spontaneous activity.

Musical hallucinations offer an opportunity to catch a glimpse of brain function in the perception and expression of music.

M Satoh

Mie St Cross Hospital, Mie, Japan

M Kokubo, S Kuzuhara

Department of Neurology, Mie University School of Medicine, Tsu, Mie, Japan

Correspondence to: Dr M Satoh, Mie St Cross Hospital, 1219-1 Shukuno, Komono, Mie-ken 510-1232, Japan; masayuki-sato@seijui-hp.jp

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References

- 1 Terao T, Matsunaga K. Musical hallucinations and palinacousis. *Psychopathology* 1999;**32**:57–9.
- 2 Berrios GE. Musical hallucinations. A historical and clinical study. *Br J Psychiatry* 1990;**156**:188–94.
- 3 Stewart L, von Kriegstein K, Warren JD, et al. Music and the brain: disorders of musical listening. *Brain* 2006;**129**(Pt 10):2533–53.
- 4 Gordon AG. Do musical hallucinations always arise from the inner ear? *Med Hypotheses* 1997;**49**:111–122.

- 5 Erkwow R, Ebel H, Kachel F, et al. ¹⁸FDG-PET and electroencephalographic findings in a patient suffering from musical hallucinations. *Nuklear Medizin* 1993;**32**:159–63.
- 6 Griffiths TD. Musical hallucinations in acquired deafness. Phenomenology and brain substrate. *Brain* 2000;**123**:2065–76.
- 7 Warren JD, Schott GD. Musical hallucinations in a musician. *J Neurol* 2006;**253**:1097–9.
- 8 Warren JD, Scott SK, Price CJ, et al. Human brain mechanisms for the early analysis of voices. *Neuroimage* 2006;**31**:1389–97.
- 9 Baba A, Hamada H, Kocha H. Musical hallucinations in schizophrenia. 2. Relations with verbal hallucinations. *Psychopathology* 2003;**36**:104–10.

Paraneoplastic limbic encephalitis associated with potassium channel antibodies: value of anti-glial nuclear antibodies in identifying the tumour

Limbic encephalitis is characterised by subacute development of short-term memory loss, seizures, confusion and psychiatric features.¹ Paraneoplastic limbic encephalitis is generally associated with small cell lung cancer (SCLC), and around 50% of patients harbour Hu, CV2/CRMP5 or amphiphysin antibodies.¹ Recently, antibodies against voltage-gated potassium channels (VGKC-abs) were identified as a new marker of a non-paraneoplastic, immunotherapy-responsive form of limbic encephalitis.^{2,3} However, the presence of VGKC-ab does not exclude a paraneoplastic cause of limbic encephalitis.¹

We described previously a new antibody called anti-glial nuclear antibody (AGNA), a marker of SCLC shown to be closely associated with paraneoplastic Lambert–Eaton myasthenic syndrome (LEMS).⁴ Here we report on two patients with paraneoplastic limbic encephalitis associated with SCLC and VGKC-ab who also presented AGNA.

Methods

The presence of AGNA was assessed by immunohistochemistry on frozen sections of paraformaldehyde-fixed rat cerebellum in nine patients with limbic encephalitis and SCLC with (n = 2) or without (n = 7) VGKC-ab, and in seven patients with non-paraneoplastic limbic encephalitis and VGKC-ab. To confirm AGNA reactivity, an immunohistochemical competition assay was performed as described previously.⁴ VGKC-abs were detected by radio-immunoprecipitation (cutoff value: 100 pmol/l).²

Case reports

A middle-aged man was admitted to hospital with a 2-week history of behavioural changes and generalised seizures. A neurological examination showed short-term memory loss, confusion and aphasia. Electroencephalography showed slowing in the left temporal lobe. Magnetic resonance imaging (MRI) of the brain showed a hyperintense signal affecting the temporal lobes on T2-weighted images. Examination of the cerebrospinal fluid showed pleocytosis (20 lymphocytes/μl). A chest x ray showed a lung mass. Histological diagnosis of SCLC was made after biopsy of an enlarged groin adenopathy. The patient was treated with valproic acid, pulses of intravenous steroids and chemotherapy, with good control of seizures and remission of the behavioural

problems and aphasia. After 6 months, in the setting of cancer progression, the patient had a relapse of limbic encephalitis (complex partial seizures and agitated behaviour) confirmed by a brain MRI. The patient was treated with repeated pulses of intravenous steroids, with good control of seizures and improvement of the agitation. He died 5 months later from cancer progression.

A middle-aged woman was admitted to hospital with a 2-month history of confusion, memory impairment and seizures. Neurological examination showed moderate short-term memory loss, mild confusion and abulia. Laboratory analysis showed hyponatraemia (118 mEq/l). Chest x ray showed a mediastinal mass confirmed by a computed tomography scan. Electroencephalography disclosed generalised slowing and epileptic activity in both temporal lobes. Cerebrospinal fluid examination and brain MRI were negative. A diagnosis of SCLC was made by transbronchial biopsy of the mediastinal lesion. Seizures did not disappear despite sodium level normalisation and treatment with multiple epilepsy drugs. Eventually the patient evolved to status epilepticus requiring intensive care and induction of barbituric coma. She died several months later from bronchopneumonia.

In both patients, the search for antineuronal antibodies (Hu, Yo, Ri, Ma1 and 2, CV2/CRMP-5, Tr, GAD, and amphiphysin) was negative. VGKC-ab levels were 170 and 220 pmol/l. On immunohistochemistry, serum from both patients showed intense labelling of the nuclei of Bergmann glia in the Purkinje cell layer of the cerebellum (fig 1). The presence of AGNA in our patients' sera was confirmed by the immunocompetition assay.

AGNA immunoreactivity was not detected in the serum of seven patients with limbic encephalitis and SCLC without VGKC-ab and seven patients with non-paraneoplastic limbic encephalitis and VGKC-ab.

Discussion

The diagnosis of classical limbic encephalitis is made in the setting of subacute onset of short-term memory loss, seizures and behavioural changes, imaging or pathological evidence of involvement of the limbic system, and exclusion of other potentially confusing diagnoses.¹ Patient 1 fulfilled the criteria for classic limbic encephalitis of definite paraneoplastic origin.¹ The clinical syndrome of patient 2 was initially attributed to a severe hyponatraemia, a common finding in limbic encephalitis associated

with VGKC-ab.^{2,3} However, when the sodium level was normalised, the clinical syndrome did not improve and the brain MRI ruled out permanent hyponatraemia-related brain damage. A normal MRI does not rule out the possibility of limbic encephalitis. Normal brain MRI, including fluid-attenuated inversion-recovery and diffusion-weighted imaging, may repeatedly be seen in patients with autopsy-proved paraneoplastic limbic encephalitis (F Graus, unpublished data).

The clinical significance of the VGKC-ab levels in our patients is not clear. Some authors consider the cut-off value in the diagnosis of VGKC-ab-associated limbic encephalitis to be 400 pmol/l,² but reports of patients with epilepsy and encephalopathy with lower titres⁵ suggest that the clinical relevance of VGKC-ab titres has to be better defined.

Our patients' sera presented AGNA defined by robust immunoreactivity with the nuclei of Bergmann glia, an astrocyte population localised in the cerebellar cortex around the Purkinje cells.⁴ We identified AGNA as a marker of SCLC rather than paraneoplastic neurological syndromes. However, we observed a tight association between AGNA and voltage-gated calcium channel antibodies in the setting of SCLC. We found that among 35 patients with SCLC and voltage-gated calcium channel antibodies (LEMS 30, paraneoplastic cerebellar degeneration 5), 18 (51%) had AGNA whereas this antibody was not detected in a series of 19 patients with non-paraneoplastic LEMS, nor in 100 of 113 patients without paraneoplastic neurological disorders and SCLC.⁴

In this study, we found AGNA in two patients with limbic encephalitis, SCLC and VGKC-ab. No AGNA reactivity was found in patients with limbic encephalitis, SCLC without VGKC-ab, or in those with non-paraneoplastic limbic encephalitis and high titres of VGKC-ab. The characteristic immunoreactivity of AGNA was not reported in any patient from the two series of patients with VGKC-associated non-paraneoplastic limbic encephalitis,^{2,3} although both were published before our description of AGNA. These data suggest that, in the setting of SCLC, the immune mechanisms that trigger AGNA are closely associated with those responsible for the generation of antibodies against neuronal membrane channels.

In conclusion, in patients with a clinical diagnosis of limbic encephalitis and positive VGKC antibodies, irrespective of the titre, the presence of AGNA should be evaluated because its detection must prompt the search for lung cancer. Future studies will confirm the association between AGNA and channel antibodies in patients with paraneoplastic neurological syndromes.

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Luigi Zuliani, Albert Saiz

Service of Neurology, Hospital Clinic, Universitat de Barcelona and Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Bruno Tavaloto

Department of Neuroscience (2 Neurologic Clinic), University of Padua, Padua, Italy

Figure 1 Frozen section of paraformaldehyde-fixed rat cerebellum immunoreacted with the serum of patient 1. There is intense labelling of the nuclei of Bergmann glia in the Purkinje cell layer typical of anti-glial nuclear antibody. Magnification $\times 200$.