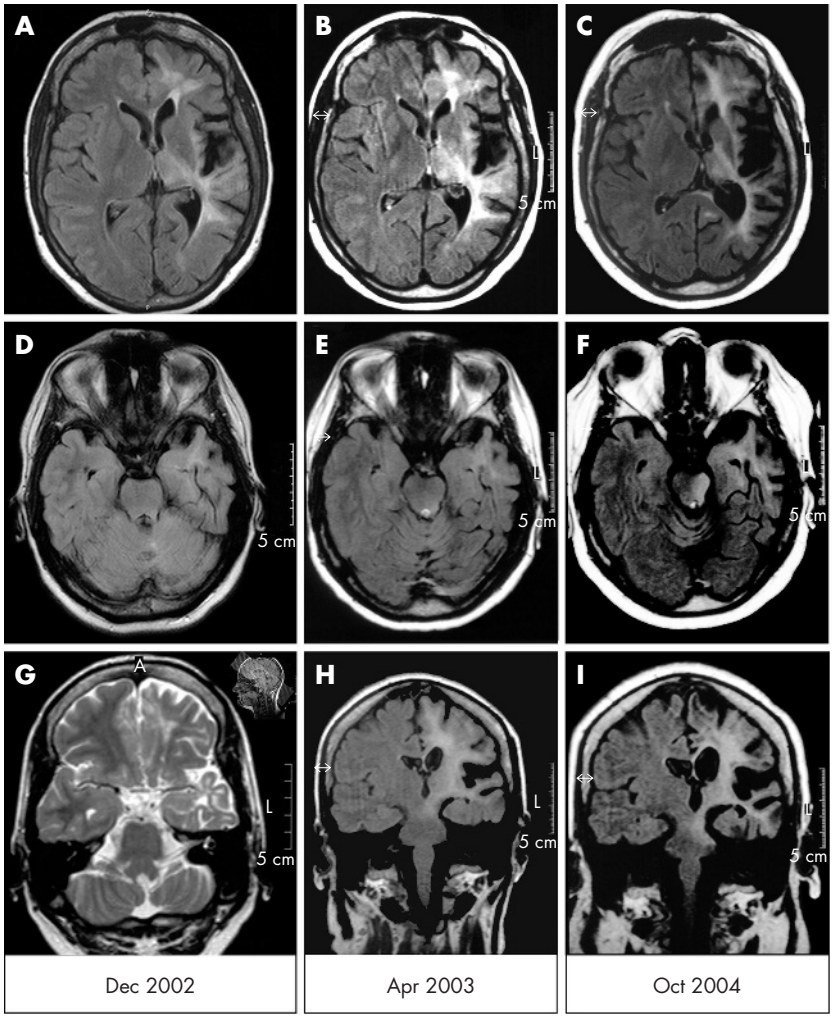

Figure 1 Serial brain fluid-attenuated inversion recovery-magnetic resonance imaging (FLAIR-MRI) scans in the patient described here. (A–C) Axial sections including the Sylvian fissure; (D–F) axial sections through the upper brain stem; (G–I) coronal sections including the pons. For the time course, see the dates on the bottom of the figure. (G) As no coronal FLAIR or T2 images from December 2002 exist, this unusually angulated T2 section showing the pons (for orientation of slices, see the small image in the upper right corner of (G)) from July 2002 is used as a substitute. A slight atrophy of the left cerebellar hemisphere is also seen.

Rasmussen encephalitis with magnetic resonance–tomographically demonstrated affection of the brain stem. The patient presented here exhibited a large increase in the fluid-attenuated inversion recovery signal, suggesting active inflammation or strong astrogliosis of the left upper brain stem in continuity with the supratentorial lesion, and clearly delineated from the right side. This is remarkable, as the characteristic and puzzling property of Rasmussen encephalitis of respecting the midline of the cerebral hemispheres is also observed here within the tight space of the brain stem. It cannot, however, be ruled out that Wallerian degeneration secondary to the supratentorial lesion contributes to this MRI presentation. The clinical improvement after resuming the immunosuppressive treatment also supports an ongoing active inflammatory process, even through the persistence of the radiological lesion. The relative mildness of the brain stem symptoms as well as the lack of topographical concordance should be noted, but does not contribute to the aetiological clarification. A possible explanation for this lower cranial nerve symptomatology without evident medullar involvement may be a supranuclear affection of the corticobulbar pathways.[4]

Infratentorial involvement in the form of cerebellar atrophy has previously been observed in childhood-onset cases, partly ipsilaterally and partly contralaterally (in the sense of a ''cerebellar diaschisis''), however, without reported clinical correlates.[5] In our patient, mild cerebellar hemiatrophy ipsilateral to the cerebral hemiatrophy without clinical correlates was observed.

To conclude, this case is an example of ongoing damage to the central nervous system, including the brain stem, even during the ''residual disease stage'', a feature indicating a late relapse of disease activity. This is particularly surprising given the fact that patients with adult-onset Rasmussen encephalitis usually experience a rather mild course and a relatively good long-term outcome.[2] This case may broaden the clinical and neuroradiological spectrum of possible courses of Rasmussen encephalitis.

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Creutzfeldt–Jakob disease in a Chinese patient with a novel seven extra-repeat insertion in *PRNP*

Familial transmissible spongiform encephalopathies comprise about 14% of all cases of transmissible spongiform encephalopathy in humans. We report on a patient with a definite diagnosis of familial Creutzfeldt–Jakob disease with an insertional mutation consisting of seven extra octapeptide repeats between codons 51 and 91 in the *PRNP* gene, associated with a genotype homozygotic for methionine at codon 129 and a novel coding change of the inserted octapeptide region.

Case report

A Chinese woman developed forgetfulness at the age of 44 years, which progressed into memory deterioration 2 years later. At age 48 years, she developed gait disturbance and was admitted to hospital. On neurological examination she presented with mild dysarthria, intellectual deterioration and cognitive dysfunction. All her extremities showed hypertonia and ataxia, and no pathological reflexes were elicited. Her general health condition was good, except for the narrowed interpalpebral fissure dimension in her left eye and poor visual acuity since childhood.

A general brain magnetic resonance image showed no remarkable changes. The first electroencephalogram showed slow wave

Codon 51									
CCT	CAG	GGC	GGT	GGT	GGC	TGG	GGG	CAG	R1
pro	gln	gly	gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R2
pro	his		gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R2
pro	his		gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R2
pro	his		gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R2
pro	his		gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R2
pro	his		gly	gly	gly	trp	gly	gln	
CCC	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R3g
pro	his		gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R2
pro	his		gly	gly	gly	trp	gly	gln	
CCC	CAT	–	GGT	GGT	GGC	TGG	GGG	CAG	R3g
pro	his		gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GAG	CAG	R2a
pro	his		gly	gly	gly	trp	glu	gln	
CCC	CAT	–	GGT	GGT	GGC	TGG	GGA	CAA	R3
pro	his		gly	gly	gly	trp	gly	gln	
CCT	CAT	–	GGT	GGT	GGC	TGG	GGT	CAG	R4
pro	his		gly	gly	gly	trp	gly	gln	
								Codon 91	

Figure 1 Nucleotide sequence of the mutant allele in the region between codons 51 and 91 of the *PRNP* of the patient. The seven extra octapeptide repeats are inserted after the second R2 cycle. The mutated nucleotide and amino acid are shown underlined. –, no amino acid in this position.

activity. The second electroencephalogram taken 13 days after admission, showed periodic sharp and slow wave complexes. Haematoxylin and eosin stain of a brain biopsy specimen taken from the left frontal lobe showed diffuse spongiform degeneration, with obvious vacuoles predominanting in the deep layers of the cortex and astrocytosis and neuronal loss in the cortical ribbon. Electron microscopy showed neurone degeneration, astrocytosis and membrane-bound vacuole. The patient's mental impairment and other neurological symptoms rapidly worsened after admission. She subsequently developed visual hallucination, urine incontinence and myoclonus 3 weeks after hospitalisation. Creutzfeldt–Jakob disease (CJD) was suspected on clinical diagnosis. She died 46 days after admission. The total illness duration was 50 months.

The patient's mother developed involuntary movements and progressive dementia at age 58 years. She was diagnosed with suspected cerebellar atrophy clinically and died 6 months after onset of symptoms. The patient's grandfather developed dementia and paralysis at age 58 years and died approximately 6 months after onset. The patient's father and four siblings were still healthy, and her only son was healthy at age 20 years.

Proteinase K resistant PrP (PrP^{res}) signals were observed on western blotting assays of 10% brain homogenate. On electrophoresis, the pattern of PrP^{res} was similar to that of PrP^{res} type 1, with predominance of monoglycosylated PrP^{res}. After deglycosylation, two prominent PrP peptides of 27 and 20–21 kDa were detected, corresponding to full-length PrP^{wt} and a C-terminal PrP fragment.

PRNP was analysed using genomic DNA extracted from the frozen brain tissue of the patient. Analysis of the polymerase chain reaction products showed that in addition to the fragment representing the full-length *PRNP*, there was an extra band approximately at position 1000 bp. Sequencing tests confirmed that the shorter polymerase chain reaction fragment was the normal human *PRNP* sequence without any mutation, and that the longer fragment contained a 168-bp insertion within the octarepeat region of *PRNP*. The 168-bp insertion was identified as a seven-extra-octarepeat sequence, composed of R2-R2-R2-R3g-R2-R3g-R2a (fig 1), in which R3g differed from wild-type R3 for a single synonymous change (A→G) at its 21st position without inducing amino acid exchange and R2a had a G→A exchange at the seventh triplet (from GGG→GAG), leading to a conversion from glycine to glutamic acid. The octarepeat region was R1-R2-R2-*R2-R2-R2-R3g-R2-R3g-R2a*-R3-R4 (insertions are shown italicised). No other mutations were detected in the PRNP open reading frame. The codon 129 genotype was homozygotic for methionine.

Comment

The patient described in this article is the first case of genetic CJD identified in China and represents the fifth reported family with a 168 bp nucleotide insertion[1–3]; however, the octarepeat sequence and gene arrangement differ from those described previously. The patient showed typical clinical features such as sporadic CJD characterised by cerebellar sign, myoclonus and dementia, but had longer illness duration than sporadic CJD. Unlike previously reported patients with familial Creutzfeldt–Jakob disease with seven-octapeptide repeat insertion, whose ages of onset ranged from 23 to 32 years and illness durations were 7–16 years,[1 4] the patient reported here presented with relatively late-onset dementia and rapid progression of clinical symptoms. It is not clear whether this is due to the novelty of the octapeptide repeat sequence, the associated mutation or some other factors, but this report indicates that the phenotype associated with seven-repeat inserts can vary.

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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 aspirin[4]). 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. ^{123}I-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 subcomponents (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 subcomponents 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.

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