Figure 1 Meta-analysis of the dbSNP:754203 CC genotype carriers. OR and 95% CI of the genotype frequencies are shown. *Autopsy confirmed sample; 54 AD cases confirmed (Ingelsson). †Early onset AD sample. n/N, number of CC genotype carriers/number of subjects. Weight %, weighting proportion in an individual study (used when combining ORs). In the separate pooled analysis of USA and European populations, a pooled effect of CC genotype frequencies was similar to those found in controls (OR 1.17; 95% CI 0.78 to 1.73 and OR 1.16; 95% CI 0.95 to 1.41, for USA and European subjects, respectively). Hardy-Weinberg equilibrium was not re-examined in studies for meta-analysis. PMID, PubMed - indexed for Medline (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>). We did not show allele frequencies of this SNP because the Alzheimer Research Forum (<http://www.alzforum.org/home.asp>) has previously published OR and 95% CI of allele frequencies of dbSNP:754203 in their meta-analysis.

levels of β amyloid and phosphorylated tau proteins.⁵ We conclude that the CYP46 intron 2 polymorphism may influence the risk of developing AD in the Finnish population, although meta-analysis does not support this role on a global scale.

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Electronic-database information

The following URLs have been mentioned in this article:
PubMed: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>; Applied Biosystems: <http://appliedbiosystems.com>; RevMan: <http://www.cc-ims.net/RevMan/>; and the Alzheimer Research Forum: <http://www.alzforum.org/home.asp>.

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Propriospinal myoclonus with life threatening tonic spasms as paraneoplastic presentation of breast cancer

Myoclonus is a sudden, shock-like, involuntary movement caused by abnormal neuronal discharges. It may be cortical, subcortical, or spinal (segmental or propriospinal).¹ One or a few contiguous spinal segments are involved in segmental myoclonus, while several segments are involved in propriospinal myoclonus since electrical activity spreads upwards and downwards from a spinal generator via propriospinal pathways. Propriospinal myoclonus may be caused by different spinal cord diseases or by drugs.^{1,2} Paraneoplastic neurological syndromes are rare immune mediated disorders associated with several types of cancer. Their pathophysiology is incompletely understood, although it is thought that specific antibodies formed against tumours may cross react with nerve cells.

Case report

A 49 year old woman presented with a 9 month history of involuntary, shock-like trunk and leg movements, occurring several times per day. Sporadically, they became prolonged, involved arm muscles, and caused transient respiratory failure. Several unsuc-

cessful therapies included clonazepam, valproate, and gabapentin.

On examination, her gait was wide based, because of fear of falling due to jerks. Tone was normal. Spontaneous sudden, brisk contractions with trunk and lower limb extension were observed. The contractions were also elicited by postural changes and sensory stimuli such as tapping for evoking reflexes. During her hospital stay, the patient daily experienced these myoclonic phenomena with isolated jerks or flurries of repetitive jerks, involving the trunk, legs, and occasionally the arms. Infrequently, they progressed into sustained and prolonged tonic contractions also involving respiratory muscles with acute respiratory failure. Resuscitation was required on two occasions.

Standard EEG, brain and spine MRI, and total body CT were unremarkable. Polymyography (fig 1A) documented single or repetitive bursts of 30–150 ms duration, with co-contraction between abdominal recti and erector spinae, and propagation up and down the spinal cord starting from the midthoracic region. Late activation of sternocleidomastoid muscle was sometimes recorded. Bursts were elicited by tactile, proprioceptive, auditory, and electrical stimuli. EEG back-averaging detected no cortical potential before movements. Needle EMG disclosed no spontaneous activity at rest in paraspinal and lower limb muscles. Long loop reflexes (LLRs) were not hyperactive. Somatosensory evoked potentials (SEPs) were of normal amplitude, although they were delayed following lower limb stimulation, and tibial nerve stimulation provoked reflex myoclonic jerks in paraspinal and leg muscles. Motor evoked potentials (MEPs) after transcranial stimulation were slightly delayed in the legs, while

lumbosacral stimulation provoked two reflex myoclonic jerks recorded in abductor hallucis: the first had constant 40 ms latency (fig 1B), incompatible with a cortical reflex loop, thus indicating a spinal generator.

CSF showed increased IgG content (6.31 mg/dl) and several oligoclonal bands, suggesting an immune mediated disorder. Serum and CSF anti-Hu antibodies were detected, but anti-Yo, anti-Ri, anti-amphiphysin, and anti-glutamic acid decarboxylase (anti-GAD) antibodies were absent. With high dose intravenous methylprednisolone, then tapered down to 50 mg/day oral prednisone, myoclonic jerks disappeared within a couple of days. One month later, CSF IgG were normal and there were few oligoclonal bands. Anti-Hu antibodies were still present but only in serum. [18F]-fluorodeoxyglucose PET disclosed abnormal uptake in right axillary nodes, which were excised. Poorly differentiated breast carcinoma presenting as axillary metastases was diagnosed; immunostaining was positive for oestrogen receptor, and negative for TTF-1 and PE-10 (both specific lung cancer markers). Whole body PET and breast MRI produced no evidence of a primary tumour.

Comment

We report the first case of paraneoplastic propriospinal myoclonus with anti-Hu antibodies. Abnormal discharges started in the midthoracic region, indicating a spinal generator. Back-averaging, normal amplitude SEPs, and normal LLRs ruled out cortical myoclonus, while lower limb SEP and MEP latency prolongation further suggested spinal cord dysfunction. Finally, since the electrical activity spread upwards and downwards with low conduction velocity (about 20 m/s), a

diagnosis of propriospinal rather than segmental myoclonus was proposed. Following anti-Hu antibody detection, breast carcinoma presenting as axillary metastases was discovered, although the primary tumour was never found. Anti-Hu antibodies are usually associated with small cell lung carcinoma (SCLC) and are highly specific for paraneoplastic encephalomyelitis and sensory neuropathy. However, they may occur with other tumours, including breast cancer, and be associated with a broader spectrum of neurological manifestations.

Life threatening tonic spasms were another feature not previously reported in association with propriospinal myoclonus, and resembled tetanus or strychnine poisoning, where stiffness may affect the respiratory muscles leading to acute respiratory failure and death.

Well defined paraneoplastic syndromes with myoclonic jerks or prolonged spasms were excluded. Opsoclonus-myoclonus syndrome is characterised by involuntary, chaotic saccades, and arrhythmic action myoclonus, probably originating in the brainstem, and involving the trunk, limbs, face, and head. In adult patients, the most common associated tumours are SCLC and breast cancer, and serum anti-Ri antibodies may be detected.³ In our case, however, brainstem myoclonus was excluded and anti-Ri antibodies were absent.

Myoclonic jerks and prolonged spasms may be superimposed on persistent rigidity involving axial and/or limb musculature in stiff person syndrome (SPS), which is electrophysiologically characterised by continuous motor unit activity despite the patient's attempts at muscle relaxation. Increased spinal excitability and spasmodic reflex myoclonus have also been reported. SPS patients may experience breathing problems if spasms and stiffness spread to respiratory muscles. Idiopathic SPS is an autoimmune disorder usually associated with anti-GAD antibodies, but SPS may be paraneoplastic, in this case being related to breast cancer and anti-amphiphysin antibodies.⁴ In our case, however, myoclonic jerks were not superimposed on rigidity, since there was neither clinical nor electrophysiological evidence of stiffness. By contrast, transient rigidity due to tonic spasms occasionally complicated these jerks. Moreover, anti-amphiphysin antibodies were absent. These findings and the myoclonus features do not support a diagnosis of paraneoplastic SPS.

Finally, hyperekplexia, a hereditary or sporadic disorder with abnormal startle response, was also ruled out. Hyperekplexia is characterised by shock-like body jerks and infrequent tonic spasms triggered by unexpected stimuli, and, differently from our case, typically consists of a brief flexion response, with facial grimacing and blinking, due to an abnormal discharge originating in the brainstem and having a rostro-caudal diffusion pattern.⁵

Strikingly, steroid treatment completely suppressed myoclonus before malignancy removal. Hence, although paraneoplastic syndromes expedite cancer diagnosis and definitive treatment, therapy of the sole neurological manifestations may also prolong survival.

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Figure 1 (A) Multi-channel surface EMG. Reflex burst elicited by electrical stimulation of left tibial nerve at the ankle (arrow head indicates stimulus artifact). Filled arrows point to burst onset in the midthoracic intercostal and paraspinal muscles; empty arrow shows the delayed spread to sternocleidomastoid muscle, indicating rostral propriospinal propagation. Electrical activity spread along the cord at about 20 m/s. Intercostal muscle EMG at 7th–8th rib; paraspinal muscle EMG 5 cm right of D1, D6, and D11 spinous processes. ITC, intercostal muscles; L, left; PSP, paraspinal muscles; QF, quadriceps femoris; R, right; RA, rectus abdominis; SCM, sternocleidomastoid. (B) MEPs elicited by magnetic lumbosacral stimulation registered from right abductor hallucis. Superimposed traces reveal normal response at 24 ms (filled arrow), followed by two anomalous high voltage responses at 40 and 110 ms after stimulus. The short latency of the first reflex burst (empty arrow) supports the hypothesis of a spinal generator. No reflex burst was registered after steroid treatment.

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A case of progressive posterior cortical atrophy (PCA) with vivid hallucination: are some ghost tales vivid hallucinations in normal people?

Patients with Parkinson's disease (PD), diffuse Lewy body disease (DLBD), or dementia with Lewy body disease (DLB) unaccompanied by paranoia, delusions, REM sleep behaviour disorder, or an obvious sleep problem sometimes report experiencing extremely vivid visual hallucinations (VH) of ghosts or monsters.^{1,2} Here we describe two VH experienced by a patient with progressive posterior cortical atrophy (PCA) which are similar to Japanese folktales and personal ghost stories.

Case report

The patient was a 60 year old man who complained that he had begun to see ghosts frequently. He noted difficulty in writing when he was 57 years old because he could not remember Japanese characters well, and this was accompanied by severe insomnia. He frequently had VH both during the day and at night. Two typical hallucinations are described below.

(1) The patient was at home when suddenly six people broke into his living room and started cooking silently. He asked them

why they had come and what they were doing, but no one answered. He questioned them repeatedly and tried to tap one on the shoulder, but as soon as his hand touched the ghost's shoulder, they all vanished instantaneously.

(2) One night, when the patient went to the toilet, he found his wife lying in the corridor stabbed to death and bleeding profusely. Although it was midnight and completely dark, he could see the fresh blood coming out of her neck wound. He was astonished and tried to help her up, but all images vanished as soon as he touched her.

Neurological examination showed Bálint syndrome accompanied by dressing apraxia, constructional apraxia, agraphia, and dyscalculia. The patient's mini-mental state examination (MMSE) score was 17/30. He showed no bradykinesia, muscle rigidity, or finger tremor. He was also seen by a psychologist who found no emotional problems. MRI revealed bilateral parieto-occipital, occipital, and mild left temporal cortical atrophy (fig 1), and cerebral perfusion estimated by xenon CT perfusion showed decreased cerebral blood flow in the bilateral parietal and frontal regions. CSF showed no abnormality. Administration of 10 mg/day of propricyazine ameliorated the VH.

The VH experienced by this patient resembles a ghost story published by the Japanese essayist Shinya Nishimaru nearly 50 years ago.³ One night when he was 23 years old, Shinya Nishimaru encountered a lady leaning against a concrete wall outside a factory. Although it was a dark, moonless night, he noticed the pattern of her clothes and outlines of her face and eyes precisely. At first, she appeared in the open air, but after 1 year began appear beside his bed. When he tried to touch her or hit her with a club, she disappeared as soon as he touched her clothes. One night, she suddenly looked him in the eye which really frightened him. He could hardly sleep a wink for several days,

which made him fear for his life, so he fled the town. (A longer version of this story together with other ghost stories can be found in the supplemental information available at <http://www.jnnp.com/supplemental>.)

This hallucination is characterised by (i) the ghost appearing without any relation to sleep at first, (ii) purely visual hallucinations (that is, the ghost never talked or tried to touch him, and the image of the ghost was very clear), and (iii) the ghost vanishing when he tried to touch it. He consulted a psychiatrist but was diagnosed as sane. However, he later saw another vivid ghost while he was mountain climbing.

We also found ghost tales resembling the VH of our case in a record of authentic Japanese folklore written almost 100 years ago. *Toh-no Monogatari* (The 'Toh-no' Folktales) edited by Kunio Yanagida, a famous Japanese folklorist, evaluated more than 300 short verbatim records of face to face encounters from old Japanese folklore, especially those involving traditional Japanese monsters, goblins, and elves. In *Toh-no Monogatari*, we also found two other stories that referred to VH of ghosts, although both of them were experienced by children.⁴

Discussion

Although neuropathological examinations were not performed, our patient was diagnosed as having PCA with VH and the cause was considered to be DLBD or Alzheimer's disease on the basis of the clinical symptoms.^{1,5}

The VH of this patient are quite similar to descriptions in Japanese folktales and personal ghost stories. When we investigated these stories from a neurological point of view, we noted several similarities between the stories and the VH common in patients with DLBD, PD, DLB, or Charles Bonnet syndrome (CBS).¹ VH is usually considered one of the clinical symptoms of DLBD, PD with late

Figure 1 MRI imaging of patient. T1 and T2 images show bilateral parieto-occipital, occipital, and mild left temporal atrophy in horizontal (A) and coronal (B) sections.