

Family pedigree. Circles = women; squares = men; open = unaffected; black = affected. Arrow indicates the proband.

The figure shows the family pedigree. Her mother (I-2) had an ataxic gait. Her siblings comprised three males and three females. Among the six, one sister (II-1), one brother (II-2), and the proband (II-5) were affected. Her sister's (II-1) gait became shuffling at the age of 25 years, and a neurological examination conducted by one of us (TH) when she was 48 years old disclosed nystagmus, slow and slurred speech, limb dysmetria, and exaggerated deep tendon reflexes with Babinski's signs. Her brother's (II-2) gait became shuffling, similar to that of his sister (II-1) at the age of 33 years. One sister (II-4) was unaffected. One brother (II-6) was mentally retarded, without spastic gait or ataxia, at the age of 36. The other brother (II-3), had been mentally retarded since childhood, and had died in a traffic accident at the age of 20.

On neurological examination of the proband (II-5), her mental status showed low grade disorder, with a mini mental state examination score of 21/30. Her speech was slightly slow but not slurred or scanned. Ocular movement was full, with poor vertical optokinetic nystagmus and nystagmus on bilateral gaze. There were no bulging eyes, fasciculation, myokymia, or dystonia. Spasticity and pronounced hyperreflexia were evident in all four limbs, being more severe in the lower limbs, with bilateral ankle clonus and extensor plantar responses. The gait was spastic, with pes cavus. There was no dysmetria or decomposition in the finger-nose test, and no autonomic dysfunction was noted. Motor and sensory nerve conduction velocities were not delayed. Brain CT and MRI showed no atrophy of the midbrain, pons, or cerebellum.

Genetic diagnosis was performed for Machado-Joseph disease with informed consent. A polymerase chain reaction (PCR) was carried out to amplify the CAG repeat using the primer MJD25/MJD52 as described elsewhere.<sup>2</sup> To confirm the sequence of MJD1, the PCR products were subcloned into the cloning site of the pCRTMII plasmid, using original TA cloning kits (Invitrogen). The inserted segments were sequenced using Sequenase ver 2.0 (TOYOBO). CAG repeat lengths were counted according to original methods<sup>2</sup>: the expanded CAG repeat included interrupted triplets of CAA. The present patient (II-5) and her sister (II-1) had expanded CAG repeats, whereas her asymptomatic brother (II-6) had no expansion. The repeat lengths of the patient (II-5), her symptomatic sister (II-1), and asymptomatic brother (II-6) were 74/14, 72/14, and 25/14 respectively.

The present patient, who was diagnosed genetically as having Machado-Joseph dis-

ease, manifested prominent spastic paraparesis. Because of poor information on their neurological status, the clinical subtype of two affected members (I-2 and II-2) is unclear, but another one (II-1) showed ataxia and spasticity, which may correspond to type II Machado-Joseph disease. By contrast, the proband could not be classified into any clinical subtypes. To our knowledge, few patients with Machado-Joseph disease present with isolated spastic paraparesis.<sup>5</sup> The unique clinical features of this patient could not be ascribed to racial differences because phenotypic variations among cases of Japanese Machado-Joseph disease are similar to those in other countries.<sup>2-4</sup>

The proband (II-5) had mental retardation, whereas other affected members with Machado-Joseph disease (I-2, II-1, and II-2) did not show any history of mental retardation. Also, other mentally retarded siblings (II-3 and II-6) had no signs of Machado-Joseph disease. Furthermore, the onset of mental disorder (II-3 and II-5) was earlier than that of signs of Machado-Joseph disease in affected members and the course of mental disorder was not progressive, being different from that of Machado-Joseph disease. It is evident that mental handicap seen in this family is not linked with signs of Machado-Joseph disease.

If the repeat size of the mutation is small in a patient, the age at clinical onset will be delayed and the neurological deficits less severe.<sup>2-4</sup> Our proband (II-5) had 74 repeats, which is not a small expansion for Machado-Joseph disease. The CAG repeat length for her elder sister (II-1), who presented with ataxia and spasticity, was not longer than this.

Sakai and Kawakami<sup>5</sup> described two patients with Machado-Joseph disease with isolated spastic paraplegia, and proposed a new subtype of this condition. Although the marriage of their parents was consanguineous, the MJD1 gene locus was heterozygous on analysis. Some inherited factor might have modified the clinical features of their pedigree, but the pedigree we examined had no blood relationship. Our case and the case of Sakai and Kawakami<sup>5</sup> might essentially fall into the same phenotype of Machado-Joseph disease.

In cases of inherited spastic tetraparesis, Machado-Joseph disease should also be suspected.

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### Playing piano in visuospatial neglect: a case study

Patients with unilateral visuospatial neglect syndrome are typically characterised by the inability to recognise or respond to stimuli presented in contralesional space. There is much disjointed information on visuospatial neglect, one of the most striking phenomena after a non-dominant hemispheric lesion.<sup>1,2</sup> Hemineglect syndrome has been found after injury to the right parietal lobe, and less often after damage to the non-dominant frontal lobe.<sup>3</sup> We describe a patient with left unilateral neglect who was able to play the piano.

A 71 year old, right handed man sustained a right hemispheric stroke and was admitted to the acute care hospital with left hemiplegia and evident left visuospatial neglect. His medical history showed hypertension, coronary artery disease and chronic gastritis, but not previous cerebrovascular events. Before the stroke, he was totally independent, working as a musician and composer. Brain CT showed an infarction of the right lateral frontal lobe (fig 1). During his stay in hospital the weakness improved in the left arm and leg, and the patient rapidly made a full recovery from the hemiplegia.

The left neglect persisted for three months after the acute event, and was confirmed by three diagnostic tasks. Firstly, when asked to identify the midpoint of 20 horizontal lines of three different lengths (100, 140, and 180 mm) drawn on a single sheet of white paper, the patient presented a 33% deviation of the bisection to the right of the centre. Secondly, when the patient was requested to copy a series of geometric items (star, cube, and house), he made an accurate depiction of the right side of the figures but neglected many details on the left side, without any awareness that the copy was incomplete. Thirdly, when a line crossing cancellation test was administered, the patient crossed the targets on the right side of the paper, forgetting 72% of those on the left side. Thus, according to established clinical criteria, our patient showed characteristic left visuospatial neglect.<sup>4</sup>

The patient also underwent an extensive neuropsychological assessment to explore different cognitive domains—namely, verbal

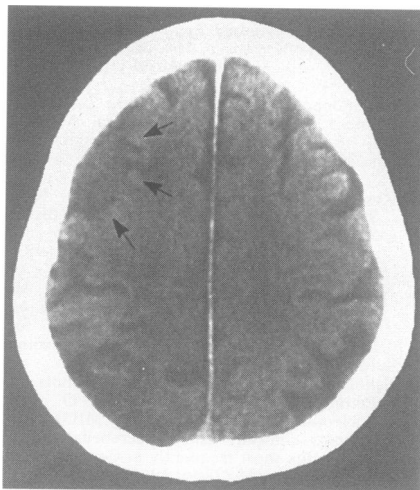


Figure 1 Brain CT showing a low density area involving the frontal right lobe.

attainment (phonological and semantic word fluency, sentence construction test); verbal memory (Rey's 15 word memory test); visual memory (immediate visual memory test); and abstract thinking (simple analogies, Raven's coloured progressive matrices). The overall cognitive performance was measured by the mental deterioration battery<sup>5</sup> which takes into account results obtained on eight tests: phonological word fluency, sentence construction, short term recall, delayed recall, immediate visual memory, simple copy, copy with landmarks, and Raven's coloured matrices. The global cognitive performance was normal. As expected, of the individual cognitive tasks, only the simple copy and copy with landmarks were abnormal.

The most interesting findings were made assessing his ability to play the piano and write music. The patient was requested to play what he saw on one page of unfamiliar music using both hands. Next, he was instructed to search for and cross out all the

notes previously played, with a pencil in his right hand and without a time limit. The sheet of music was placed with respect to the midline of his body and this placement was held constant across all the different tasks. Almost without exception, the patient accurately played all notes on both sides of the page, using the entire keyboard and all pedals appropriately. Despite this good performance, when asked to cross out the notes he had just played, he cancelled the notes on the right side of the page and neglected 75% of those on the left side. Moreover, when he attempted to write a new musical theme or a simple scale, he again omitted the left side of the page (fig 2). To better understand the patient's awareness of the notes on the left side of the page, the patient was requested to sing the musical pieces before playing them. Again, when singing he did not neglect words or notes on the left side.

Unilateral visuospatial neglect syndrome is characterised by a broad range of presentations that may be apparent only during specific situations or when performing different tasks. More commonly, it is not an "all or none phenomenon", such that separate tests may not identify the neglect syndrome in all patients.<sup>4</sup> Additionally, single deficits are not always evident with the same aspect and extent during different tasks.<sup>6</sup>

According to other authors,<sup>7</sup> patients with non-dominant right lobe injury may be unable to focus their attention on single components on the left side of a global figure, yet they may have a well structured global perception. These patients have an implicit awareness of stimuli that are not separately perceived and identified. Our patient's neglect was particularly evident when focal attention was concentrated on single elements of a more complex presentation. As shown by his capacity to play the piano and to sing music, our patient could have a global perception of the music but he was clearly unable to shift his attention on single notes. The modularity of music perception and reproduction has previously

been shown.<sup>8</sup> Indeed, it has been suggested that musical competence might be shifted to the left hemisphere in persons with higher musical education.<sup>9</sup> Perhaps, our patient's neglect was similar to that of a patient recently described by Marshall and Halligan: "He can perceive the whole forest, but only half the trees".<sup>10</sup> Interestingly, whereas the patient described by Marshall and Halligan showed both parietal and frontal lesions, CT of our patient showed only a frontal infarction, which may represent the real culprit in this syndrome.

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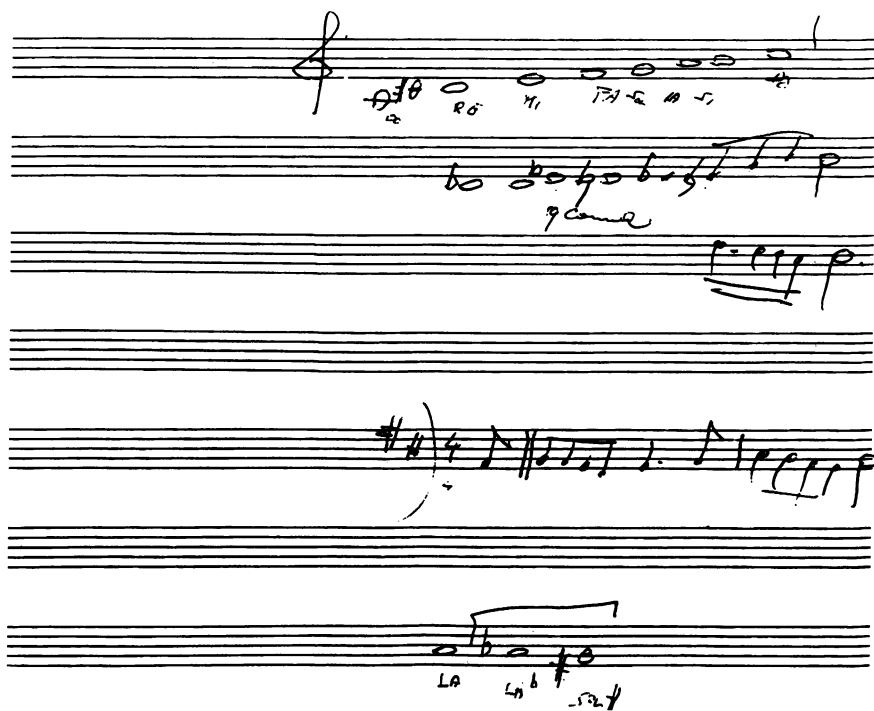


Figure 2 The patient's attempts to write a musical scale (top) and to draft a composition. Both series were begun from the centre of the page. The left hand side was systematically ignored.

## Two unusual clinical presentations of the mitochondrial DNA A3243G point mutation in adult neurological practice

The most often identified mitochondrial tRNA gene point mutation is at position 3243 (A to G) in the mitochondrial transfer RNA gene for leucine (UUR). It was originally described in association with the mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) phenotype, but is increasingly recognised to occur in association with other phenotypes. Disease associated with this point mutation presents in childhood or early adult life in the vast majority of cases and there are often other affected family members in the matrilineal line.<sup>1-3</sup> In this report we describe two patients presenting with unusual phenotypes over the age of 50 years without any family history. We highlight the importance of considering mitochondrial disease associated with this mutation in this age group and show that it may have important investigative and prognostic implications.

Patient 1 was a right handed 51 year old man who presented with a three day history of progressive difficulty using his left side, and left sided inattention. A year previously he had presented with a nocturnal seizure and