

Table 1 Heart rate variability in panic disorder and controls

	Patients (n = 10)	Controls (n = 10)
W:		
LF (nu)	67.9 (11.1)*	53.2 (7.3)
HF (nu)	32.1 (8.1)*	42.7 (4.9)
LF/HF	2.33 (0.88)*	1.28 (0.21)
Stage 2 non-REM sleep:		
LF (nu)	39.9 (13.9)	36.2 (15.5)
HF (nu)	60.1 (15.2)	57.3 (11.2)
LF/HF	0.84 (0.63)	0.76 (0.48)
Stage 3-4 non-REM sleep:		
LF (nu)	26.9 (11.1)	25.9 (8.6)
HF (nu)	73.1 (14.6)	66.2 (11.6)
LF/HF	0.47 (0.41)	0.46 (0.32)
REM sleep:		
LF (nu)	56.3 (12.8)	53.2 (16.6)
HF (nu)	43.7 (8.3)	41.5 (14.2)
LF/HF	1.53 (0.68)	1.83 (1.26)

Values are means (SD). W = wakefulness before sleep; nu = normalised units.

*P < 0.04 v controls.

trend both in patients with panic disorder and controls (table). During REM sleep, an increase in sympathetic activity occurred almost to the value of wakefulness, both in patients and controls. These conclusions are corroborated by the LF/HF ratios, which showed a sympathetic preponderance during REM sleep and a parasympathetic preponderance during non-REM sleep stages in both groups. No difference was found between patients and controls in LF, HF, and LF/HF ratio during sleep, whereas an increased LF and a decreased HF were found in patients during wakefulness before sleep.

Our nocturnal findings do not suggest autonomic dysfunction in panic disorder. However, our data do not exclude a role of the autonomic nervous system in the pathophysiology of panic disorder. In fact, our study shows that patients with panic disorder have sympathetic overactivity (and cholinergic underactivity) during wakefulness before sleep. Thus an intrinsic defect in autonomic regulation may be excluded in panic disorder, but these patients have a higher sympathetic tone than controls during the awake state, probably dependent on cognitive activity. This diurnal increase in cardiac sympathetic activity could play a part in fatal cardiac arrhythmias in panic disorder, as recently suggested.⁶

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Large deletion (7.2 kb) of mitochondrial DNA with novel boundaries in a case of progressive external ophthalmoplegia

Chronic progressive external ophthalmoplegia (CPEO)^{1,2} is a well characterised form of mitochondrial myopathy; it occurs with single or multiple deletions of mitochondrial DNA (mtDNA), or with the 3243 point mutation.¹ Single deletions occur sporadically and are usually not transmitted to offspring, whereas point mutations are transmitted maternally and multiple deletions are inherited in an autosomal way. Single deletions are often flanked by direct repeats of three to 18 base pairs (bp).¹ The "common deletion"¹⁻³ found in one half of patients with CPEO is 4.9 kb long and occurs between direct tandem repeats at positions 8470-8482 and 13 447-13 459.³ A partial duplication of mtDNA can be associated with the deletion and was reported to be specific for Kearns-Sayre syndrome.⁴ We describe a young woman with a sporadic CPEO and a large deletion (7.2 kb) of mitochondrial DNA with novel boundaries, flanked by a 14 bp imperfect tandem repeat at positions 8407-8420 and 15 658-15 671.

A 28 year old woman was referred to us for investigation of CPEO. At the age of 12 she developed a progressive ptosis of the left eyelid. A contralateral ptosis appeared two years later, with a fluctuating vertical diplopia. Since then, progressive ophthalmoplegia was noticed. Subjectively there was no limb weakness; she did not have nyctalopia, or cardiac arrhythmia. Her family history was negative for neuromuscular disorders, diabetes, and hearing impairment. Relatives were not examined.

Neurological examination confirmed bilateral ptosis, and severe limitation of eye movements in all directions during voluntary and reflex movements. Visual acuity was 6/15 in the right eye and 6/10 in the left; fundus was normal. Hearing was not impaired. There was a mild facial paresis affecting predominantly the orbicular palpebral muscles, and moderate paresis of the trapezius and sternocleidomastoid muscles. Muscle strength was slightly reduced proximally and distally in the four limbs. Tendon

jerks and detailed sensory testing were normal.

Electromyography showed a full recruitment on submaximal effort with polyphasic potentials in the examined muscles (right arm and right leg) suggesting a myopathy, whereas nerve conduction studies were within the normal range. An ECG was normal. Lumbar puncture was not performed. Brain CT was normal. There was a moderate rise of creatine kinase and lactate dehydrogenase concentrations. Diabetes mellitus was not present.

Quadriceps muscle biopsy showed an increased variability in the size of fibres; few fibres showed subsarcolemmal accumulation of mitochondria, without a typical ragged red pattern on trichrome-Gomori staining. Few fibres were cytochrome oxidase negative. Electron microscopy showed paracrystalline mitochondrial inclusions. Enzymatic activity of the respiratory chain complexes (I to IV) was within the normal range. When compared with citrate synthase, complex III activity was slightly reduced (6% of citrate synthase activity, normal range, 10-53%, n = 25).

Total DNA was extracted from muscle and blood by standard techniques. Southern blot analysis of total muscle DNA digested with PvuII and hybridised with a polymerase chain reaction (PCR) generated tRNA^{Leu} (UUR) probe (3130-3558) disclosed an additional band of approximately 9 kb in length (figure, A), suggesting the presence of a large deletion of mitochondrial DNA. The mean (SD) proportion of mutant versus total amount of mtDNA evaluated by scanning densitometry was 51 (4)% (n = 3). The deletion was present in 51% of mitochondrial DNA molecules in deltoid muscle but it was absent from leucocyte mitochondrial DNA. The presence of an associated duplication was ruled out by digestion of total DNA with BamHI, which cuts within the deletion. Hybridisation with the tRNA^{Leu}(UUR) probe (figure, A) showed two slower migrating bands, whereas a probe (11 713-11 832) lying within the deletion only hybridised to the 16.5 kb band (figure, B). (Double digestion with SnaBI and BglII gave similar results, data not shown.) Therefore, the two upper bands do not contain the full length wild type sequence, and cannot be duplications, but most likely are a circular deletion monomer (CDM) and circular deletion dimer (CDD).² Amplification by PCR with primers flanking the "common" deletion³ yielded a 5 kb fragment in leucocyte DNA amplified from wild type DNA. Muscle DNA amplification yielded an additional 1 kb fragment (not shown). This fragment was cloned in a pT7 blue vector (NovagenTM); The DNA sequence was determined in an automated sequencer (ALFTM) to map precisely the deletion. The length of the deletion was 7.2 kb and it was flanked by a 14 bp imperfect tandem repeat at positions 8407-8420 and 15 658-15 671. (Figure, C).

Surprisingly, sequence analysis also showed that primer H2³ did not prime where expected (13 506-13 255) but hybridised instead at position 16 248-16 255 where there is a perfect homology over eight nucleotides at the 3' end.

The phenotype of the patient suggested a mitochondrial myopathy. Analysis of DNA showed a large deletion of mitochondrial DNA with novel boundaries. Similar deletions are described with similar phenotypes and not with healthy controls, strongly sug-

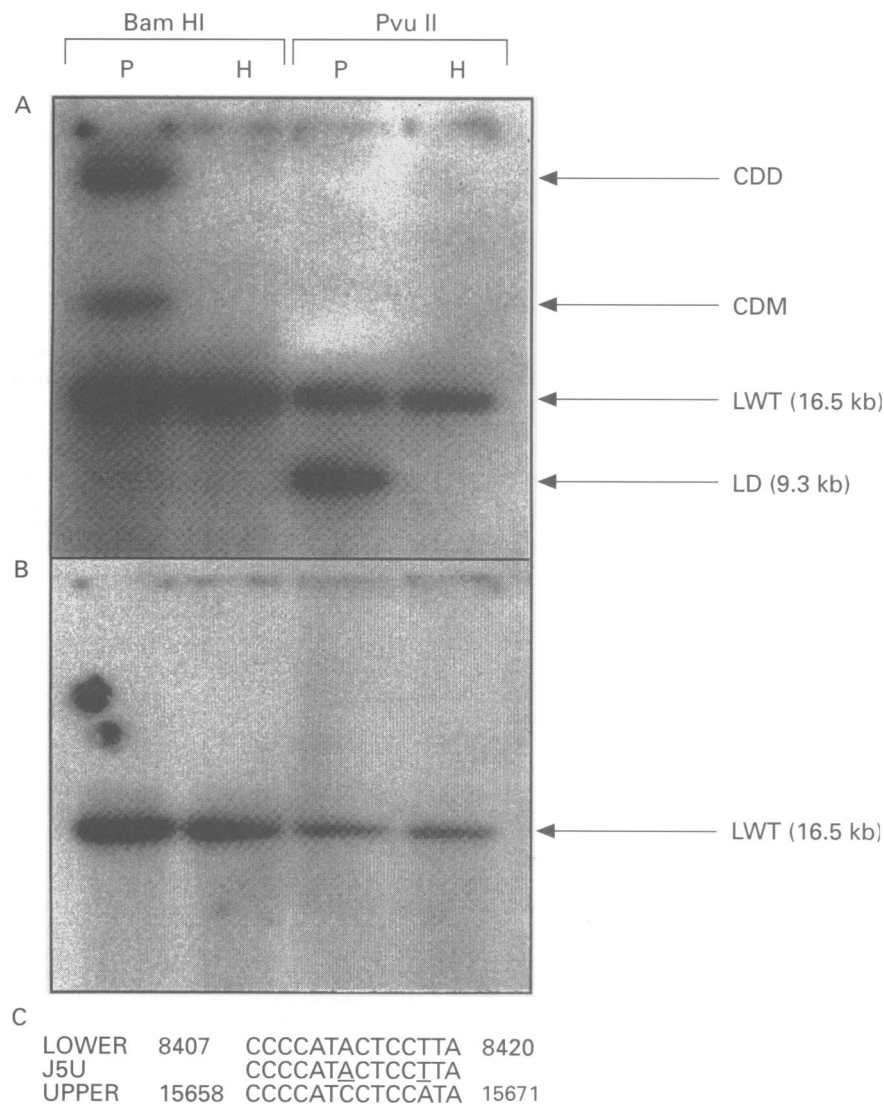


Figure 1 Southern blot analysis of muscle DNA of the patient (P) and of a healthy control (H), digested with PvuII and BamHI, and hybridised to a mitochondrial tRNA^{Leu(UUR)} probe (A), which detects all mtDNA. The PvuII digest of the patient DNA shows a 16.5 kb band (LWT) and an additional slower migrating bands (CDM, CDD) that are not seen when the same filter is hybridised with a probe lying within the deletion (B) and that only detects wild type and duplicated molecules, therefore ruling out the coexistence of a duplication. LWT = linear wild type; LD = linear deleted; CDM = circular deletion monomer; CDD = circular deletion dimer. In the wild type sequence there is an imperfect tandem repeat of 14 base pairs in length (C), flanking the deletion. In the mutant DNA (clone J5U) only one copy of the repeat is present and the sequence is identical to the "lower" sequence. Mismatches are underlined. Numbers refer to nucleotide positions of mtDNA.

gesting that the deletion is responsible for the myopathy. There was no associated duplication, in accordance with Poulton *et al.*,⁴ who showed that duplications are characteristic of Kearns-Sayre syndrome. The deletion was flanked by a 14 bp imperfect tandem repeat at positions 8407–8420 and 15 658–15 671. It encompassed nine genes encoding subunits of the complexes I, III, IV, and V of the respiratory chain, as well as six tRNA genes. So far no deletion has been mapped with these boundaries.⁵ There is a correlation between the percentage of deleted mtDNA and the severity of the myopathy: a recent study⁶ showed 31 (26)% of mutant DNA in unaffected muscles and up to 95% of deleted molecules in affected muscles. With 51% of mutant versus total mtDNA in a very mildly affected muscle our results are in accordance with the above survey. The assay for enzymatic activity of the respiratory chain was normal showing that a large deletion, with a proportion of 51% of

mutant mtDNA in the biopsied muscle is compatible with normal respiratory chain activity.

Histologically signs of a mild myopathy were apparent, with few cytochrome oxidase negative fibres. There were no ragged red fibres, consistent with the fact that these may be absent in established mitochondrial encephalomyopathies.¹

The mitochondrial DNA deletion was not present in leucocytes, showing the need for a muscle biopsy to prove the genetic defect.

We thank Dr Melanie Price for critical reading of the manuscript, Professor Franco Regli for supporting this project, Sophie Devrient for technical assistance, and Dr Alexandre Lobrinus for the ultrastructural analysis.

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Pure word deafness after resection of a tectal plate glioma with preservation of wave V of brain stem auditory evoked potentials

Pure word deafness from brainstem lesions is uncommon because of the bilateral representation of the auditory system within the brainstem.^{1,2} The unique involvement of the inferior colliculi in cases of word deafness in which other anatomically close structures of the auditory system had been spared has only been reported twice.

It is generally accepted that the inferior colliculus is the generator of wave V of brainstem auditory evoked potentials (BAEPs) and that its bilateral destruction will inevitably lead to abnormalities in their recording.^{1,3} Bilateral destruction of the inferior colliculi with preserved wave V of BAEP in humans has not been described to our knowledge.

Here we report a patient in whom a circumscriptive lesion of both inferior colliculi has led to the isolated neurological deficit of pure word deafness with repeatedly documented preservation of wave V of BAEPs.

This 36 year old Turkish patient developed progressive signs of raised intracranial pressure at the age of 28, was diagnosed as having obstructive hydrocephalus, and was shunted. On CT one year before admission a pineal region mass was described for the first time. This showed pronounced enhancement on MRI and occupied the dorsal midbrain with exophytic growth. His neurological examination was normal apart from a reduced visual acuity. Speech audiogram, pure tone audiogram, and BAEPs were normal.

The lesion was attacked via a infratentorial-supracerebellar approach. The inferior colliculi could not be identified during surgery. Complete removal was documented on postoperative MRI as well as the destruction of both inferior colliculi (figure). Histology disclosed a pilocytic astrocytoma grade I.