Tooth disease with CNS involvement as shown by electrophysiological studies and the presence of myelin lesions in brain MRI. In our patients point mutations were identified in GJB1, a gene coding for connexin 32 (GenBank acc number 117688). We also point to the possible importance of the position (intracellular or extracellular) of the mutations in the involvement or not of the CNS.

In the process of investigating a panel of patients with Charcot-Marie-Tooth disease for mutations leading to the disease, we have screened the GJB1 gene for mutations in six patients (C12, C64, C10, and C13 (all unrelated), and C2-1 and C2-2 (brothers) who did not have a CMT1A duplication and had a family history compatible with an X linked mode of transmission. GJB1 is a gene coding for connexin 32 (Cx32), a gap junction protein that is found in both the peripheral and the central nervous systems² and that has been reported by many to be responsible for CMTX, the X linked subtype of Charcot-Marie-Tooth disease. We performed our search using SSCP and nucleotide sequencing when additional bands were detected.³ Mutations leading to amino acid sequence changes and transmitted with the disease were detected in all six patients, whereas these nucleotide variations were not detected in 150 healthy control X chromosomes. Because Cx32 is a protein expressed in both the peripheral and the central nervous systems we proceeded to test for CNS involvement in those patients using electrophysiological (table) and MRI techniques. The clinical and laboratory findings for our patients were as follows.

Patient C2-1, a 19 year old man, had a history of 5 hour to 3 day long episodes of weakness—generalised or at other times localised to the left or right half of the body—dysarthria, and difficulty in swallowing. Neurological clinical examination showed muscle weakness and peripheral atrophy of the limbs, absence of tendon reflexes, distal loss of vibration in the legs, indifferent plantar response, and bilateral pes cavus. The CSF was normal. Brain SPECT (Tc-99m HMPAO {15 mCi}) showed significant reduction of blood flow in the left parietal lobe. Brain MRI showed bilateral symmetric areas in the central white matter supraventricularly with high intensity signal in T2 weighted

images. Electrophysiological studies (table) showed that both the central and peripheral nervous systems were affected. The patient had a C to T transition at position 164 (novel mutation).

Patient C2-2, the 21 year old brother of C2-1, had the same symptoms (multiple episodes of muscle weakness) since the age of 10 years. The clinical findings were also the same. In this case the CSF showed IgG oligoclonal bands. Brain MRI was normal. Electrophysiological studies also showed that both the central and peripheral nervous systems were affected. The patient had the same mutation as his brother C2-1, as was expected.

Patient C12, a 63 year old man, had progressive muscle weakness and peripheral atrophy of the extremities since the age of 9 years. When admitted he had severe muscle weakness, absence of tendon reflexes, distal loss of vibration in the legs, dysmetria, fine tremor, positive Romberg's sign, and bilateral pes cavus. The CSF showed an IgG index of 1.0 (normal<0.85) and oligoclonal bands. Brain MRI showed foci of demyelination in the white matter of the cerebral hemispheres. Electrophysiological studies also showed that both the central and peripheral nervous system were affected. The patient had the same mutation as patient C2-1.

Patient C64, a 58 year old man, presented with progressive muscle weakness and peripheral atrophy since the age of 10 years. His CSF was not sampled. Brain MRI showed high density areas of demyelination in the white matter on the left side in the frontoparietal area. The patient had a G to A transition at position 491 (novel mutation).

Patient C10, a 78 year old man, presented with progressive muscle weakness and peripheral atrophy of the legs since the age of 11. The clinical picture was the same as that of patient C64. The CSF and brain MRI were normal. The patient had a T to A transition at position 359 (novel).

Patient C13, a 40 year old man, presented with progressive muscle weakness and peripheral atrophy starting at the age of 7 years. His CSF and brain MRI were normal. The patient had a C to T transition at position 43 (already reported⁴). Sural nerve biopsy performed in patients C2-1, C2-2, C64, and C10 showed loss of muscle fibres and "onion bulb" formation. It is of particular interest,

possibly implying an underlying mechanism, that the four patients with evidence of CNS involvement (C2-1, C2-2, C12, and C64) had mutations in the extracellular domain of Cx32, and by contrast, in the two patients with no evidence of CNS involvement (C10, C13) the mutations were in the intracellular domain of the protein.

The exact pathogenetic mechanisms of the various types of myelin damage are not yet fully understood. Therefore, we cannot reach any convincing conclusions about the possible relations between those degenerative processes and the position of Cx32 mutations. However, we hope that our findings will contribute to a better understanding of some myelin damage mechanisms.

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Lack of mutation G209A in the α -synuclein gene in French patients with familial and sporadic Parkinson's disease

Polymeropoulos *et al* described the genetic linkage of a large Italian Parkinson's disease pedigree (Contursi) to chromosome 4q21-q23¹; more recently the sequence of the α -synuclein gene located in this chromosomal region in affected patients from this kindred disclosed that most of the affected members were heterozygous for a missense mutation (alanine→threonine) at position 53 of the protein.² This same missense mutation was also found in three additional unrelated families of Greek origin with Parkinson's disease.

The mutation was found by DNA sequence analysis of the fourth exon of the α -synuclein gene, disclosing a single base pair change at position 209 from G to A (G209A), and creating a novel *Tsp45I* restriction site. Using a polymerase chain reaction (PCR) assay and *Tsp45I* restriction, we have found some French patients with Parkinson's disease. Genomic DNA was amplified with primers 3 and 13 of the DNA sequence (GenBank ID U46898) in a 50 μ l reaction volume (10 mM Tris-HCl, pH=8.3; 50 mM KCl; 1.5 mM MgCl₂; 200 μ M of each dNTP and 1 U *Taq* polymerase); cycling parameters were: one initial step of hybridisation at 94°C during 5 minutes, 35 cycles of PCR (hybridisation at 60°C, 40 seconds, extension at 72°C, 40 seconds; denaturation at 94°C, 40 seconds) and a final extension step (5 minutes at 74°C). A 20 μ l aliquot of the 216 base pair (bp) product was restricted with the

Electrophysiological data from the six patients

		C2-1	C2-2	C12	C64	C10	C13	Normal
MNC:								
Median	Ampl (mV)	4	0.8	0.6	0.8	1.0	0.2	
	DL (ms)	4.6	4.4	6.6	5.7	4.8	8.6	
	CV (m/s)	36	33	29	31	29	21	
Peroneal	Ampl (mV)	2.5	0.4	NE	NE	NE	NE	
	DL (ms)	7.4	5.1	NE	NE	NE	NE	
	CV (m/s)	38	30	NE	NE	NE	NE	
SNC:								
Sural	Ampl (mV)	2	4	NE	0.5	NE	NE	
	DL (ms)	3.6	2.9	NE	8.1	NE	NE	
	CV (m/s)	31	31	NE	22	NE	NE	
BAERs:								
Right	I (ms)	1.58	2.20	1.82	1.68	1.52	1.41	<1.73
	III (ms)	4.54	4.58	4.63	4.61	3.12	2.89	<3.79
	V (ms)	6.14	7.22	6.87	6.24	5.25	4.97	<5.72
Left	I (ms)	1.72	1.62	1.98	1.85	1.43	1.51	<1.73
	III (ms)	4.24	4.60	4.75	4.79	2.98	3.13	<3.79
	V (ms)	6.20	6.22	7.31	6.87	4.95	4.87	<5.72
VEPs:								
Right	Lat (ms)	111.5	95.5	NP	112.2	NP	NP	80-108
	Lat (ms)	97	110	NP	110.8	NP	NP	R-L<8

MNC=Motor nerve conduction; Ampl=amplitude; DL=distal latency; CV=conduction velocity; SNC=sensory nerve conduction, BAERs=brain stem auditory evoked responses: waves I, III, and V; VEPs=visual evoked potentials; Lat=latency; NE=not evoked; NP=not performed.

Electrophoresis patterns of *Tsp45I* digestion of polymerase chain reaction (PCR) products. Lane P shows pUC19 plasmid restricted by the enzyme (the four restriction fragments at 1583, 576, 311, and 211 bp). All the nine subjects tested were wild type, producing a single 216 bp PCR product which was resistant to *Tsp45I* digestion. M=DNA size marker.

Tsp45I enzyme at 65°C for 5 hours; the efficiency of the *Tsp45I* restriction was verified by monitoring for the pUC19 plasmid restriction (four fragments at 1588, 576, 31, and 211 bp). The digested PCR products were separated by electrophoresis on a 3% agarose gel and visualised by ethidium bromide staining.

Fourteen French families^{3,4} with at least two members in each family meeting clinical criteria for idiopathic Parkinson's disease were tested. Affected members in all families exhibited at least two of the three cardinal signs of Parkinson's disease (bradykinesia, rigidity, and resting tremor), as well as marked improvement with levodopa treatment. The G209A mutation was not found in 27 patients with Parkinson's disease belonging to these 14 French pedigrees. The *Tsp45I* restriction site was also absent in the genomic amplificate of 79 patients of French origin with sporadic Parkinson's disease.

We conclude that the G209A mutation is rare, or absent, in French patients with familial and sporadic Parkinson's disease, and similar results were obtained recently from American patients.⁵ The main age at onset of disease in our patients with Parkinson's disease, both familial and sporadic, was 64.5 (range 25–88) years. The major kindred published² in which the G209A mutation was found originates in Contursi (southern Italy) and has fairly typical Parkinson's disease, albeit with relatively early onset of symptoms and rapid subsequent progression; little has been reported until now about the three Greek families with Parkinson's disease with the G209A mutation, except that they too have relatively early onset. Probably the G209A mutation concerns a small set of families with Parkinson's disease, originating from some focal localities on the Mediterranean coast.

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Resolution of extensive spinal epidural haematoma with conservative treatment

Spontaneous spinal epidural haematoma (SSEDH) is an uncommon condition presenting with local and radicular pain associated with clinical features of rapidly progressive spinal cord compression. The cause of the bleeding is varied, with anticoagulant therapy recognised to be the commonest known aetiological factor.¹ Surgery is the preferred treatment, regardless of aetiology, especially in patients with extensive haematomas and neurological deficits.^{1,2} Spontaneous resolution of the haematoma is reported but rare.^{3–5} We report a case of an extensive spontaneous spinal epidural haematoma extending from the upper cervical to lower thoracic region secondary to anticoagulant therapy, with remarkable clinical and radiological improvement with conservative management.

An 82 year old woman was admitted with a one week history of neck pain and upper thoracic pain, which had worsened during the preceding 4 days. On the day before admission, she developed sudden onset of complete paraplegia with urinary retention. She had noticed some improvement in power in her legs and back pain on the day of referral to our institution. She has a medical history of ischaemic heart disease with congestive cardiac failure and was on long term warfarin therapy for atrial fibrillation. At the referring hospital, her international normalised ratio (INR) was 10 and she was transferred to our neurosurgical unit after vitamin K and fresh frozen plasma were administered.

When assessed on arrival, she was complaining of mild thoracic pain. There was no neurological abnormality in the upper limbs. Tone was increased in the lower limbs with grade 2 (MRC) power on the left and grade 3 on the right. She had sensory loss to pin prick below D10 with saddle anaesthesia. Posterior column sensation was preserved. Deep tendon reflexes were pathologically brisk in the lower limbs and planter responses were extensor bilaterally.

Her INR was 1.9 and radiography of the cervical spine showed spondylotic changes and thoracic spine radiography showed evidence of osteoporosis. There was no fracture. Brain MRI showed an intermediate to high signal intensity epidural lesion suggestive of haematoma from C-1 extending to the lower thoracic region, compressing the dorsal aspect of the cord (figure).

As the power in her lower limbs was improving, we elected to treat her conservatively. Her clotting derangement was corrected with vitamin K and fresh frozen plasma while monitoring her INR. Her power continued to improve and at the time of her discharge she had grade 4 power in her legs with associated mild distal sensory loss. Eight weeks later, she had grade 5 power but was slightly unsteady on her feet due to spasticity. Sensory testing was normal. Repeat MRI showed almost complete resolution of the haematoma.

Cervical and thoracic MRI showing the extent of epidural haematoma.

Spontaneous spinal epidural haematoma (SSEDH) is an uncommon disorder first described by Jackson in 1869. It usually affects patients in the age group 20 to 70 and the thoracic spine is the commonest region affected. Spinal MRI is the investigation of choice in establishing diagnosis, characteristically showing increased signal intensity in T1 weighted images in an epidural mass at the first examination or increasing signal intensity with time; and in T2 weighted images, showing focal low signal intensity in early stages.⁴ The aetiology includes vascular malformations, coagulopathies, anticoagulant therapy, aspirin intake, minor trauma and hypertension.^{1,2,6} In about 40% of cases, the cause is unknown despite extensive investigations.¹ About 300 cases of SSEDH have been reported in the world literature.^{1–6} Anticoagulant therapy is the commonest known cause of SSEDH,¹ but prothrombin time or INR values do not seem to correlate with the risk of haemorrhage.^{1,6}

Surgery is generally the treatment of choice as the rapid decompression of the spinal cord ensures maximal neurological recovery. It is generally held that early (<12 hours) surgery and good preoperative neurological status promise the best possible outcome, although delayed surgery after total loss of spinal cord function does not completely exclude the possibility of some recovery.^{1–3}

We report a case of SSEDH in an 82 year old lady who was on anticoagulant therapy (warfarin), for cardiovascular disease, and presented with features of spinal cord compression associated with back pain. Spinal MRI disclosed spinal epidural haematoma extending from C-1 to the lower thoracic