LETTERS

"Sporadic" familial amyloidotic polyneuropathy in a German patient with B cell lymphocytic leukaemia

We report a 70 year old German man presenting with a three year history of progressive numbness and painful tingling and burning paraesthesiae in his hands, feet, and lower legs, which had worsened during recent months. He also reported unsteadiness of gait, fatigue, night sweats, loss of appetite, and a weight loss of 12 kg within one year. He denied bowel or bladder problems and alcohol ingestion, but admitted smoking (110 pack-years). His family history was negative for neurological diseases.

The family was originally from Gdansk (now Northern Poland). The patient's father and his four siblings all reached their 80s without developing neurological symptoms. The patient's mother died at the age of 64 of blood cancer, and her half brother died at the age of 78. Three of the patient's siblings died at the ages of 1, 17, and 33 (starvation, killed in the war, stomach cancer). Two further sisters, aged 64 and 69, their descendants, and the patient's own five sons and their children were healthy. Both of the patient's grandmothers died in their 80s, whereas the paternal grandfather died early of unknown cause, and the maternal grandfather drowned in his 30s.

Neurological examination revealed severe ataxia of gait and stance, atrophy of the small hand and foot muscles, and bilateral distal pareses (3–4/5 on the MRC scale), diminished tendon jerks, a glove and stocking distribution of hypoaesthesia for all sensory qualities up to the mid-thighs and elbows, and severe trophic skin disturbances of the lower legs and hands with oedema and ulcers, suggestive of autonomic neuropathy. No orthostatic hypotension was observed.

Quantitative sensory testing showed markedly increased or undetectable thermal thresholds for heat and cold sensation in both hands and feet. Dynamic (brush) and static (von Frey hair) mechanical stimuli were not detected. Electrodiagnostic studies revealed absent sensory nerve potentials in the right sural nerve, absent compound muscle action potentials (CMAP) of the right tibial nerve, and markedly reduced CMAP, moderately slowed conduction velocity, and no F waves in the right median nerve. An ECG showed atrial fibrillation. On transthoracic echocardiography there was concentric hypertrophy of the left ventricle, dilatation (51 mm) of the left atrium, no stenoses of the cardiac valves, and normal left ventricular function. The patient had no history of hypertension. Abdominal and thoracic computed tomography detected no tumour mass or lymph node enlargement.

Isoelectric focusing of the serum showed oligoclonal bands identified as IgG λ and κ on immunofixation. In the urine, no Bence–Jones proteinuria was detected, and creatine clearance was within normal limits. The blood leucocyte count was $7.1 \times 10^3/\mu l$, 40% of which were lymphocytes. Flow cytometric analysis of the peripheral blood showed that 38% of the lymphocytes were positive for CD19, CD5, CD23, and CD27. These cells showed normal CD20 expression and slight surface expression of λ light chains. A bone marrow biopsy showed multifocal 40% infiltration with

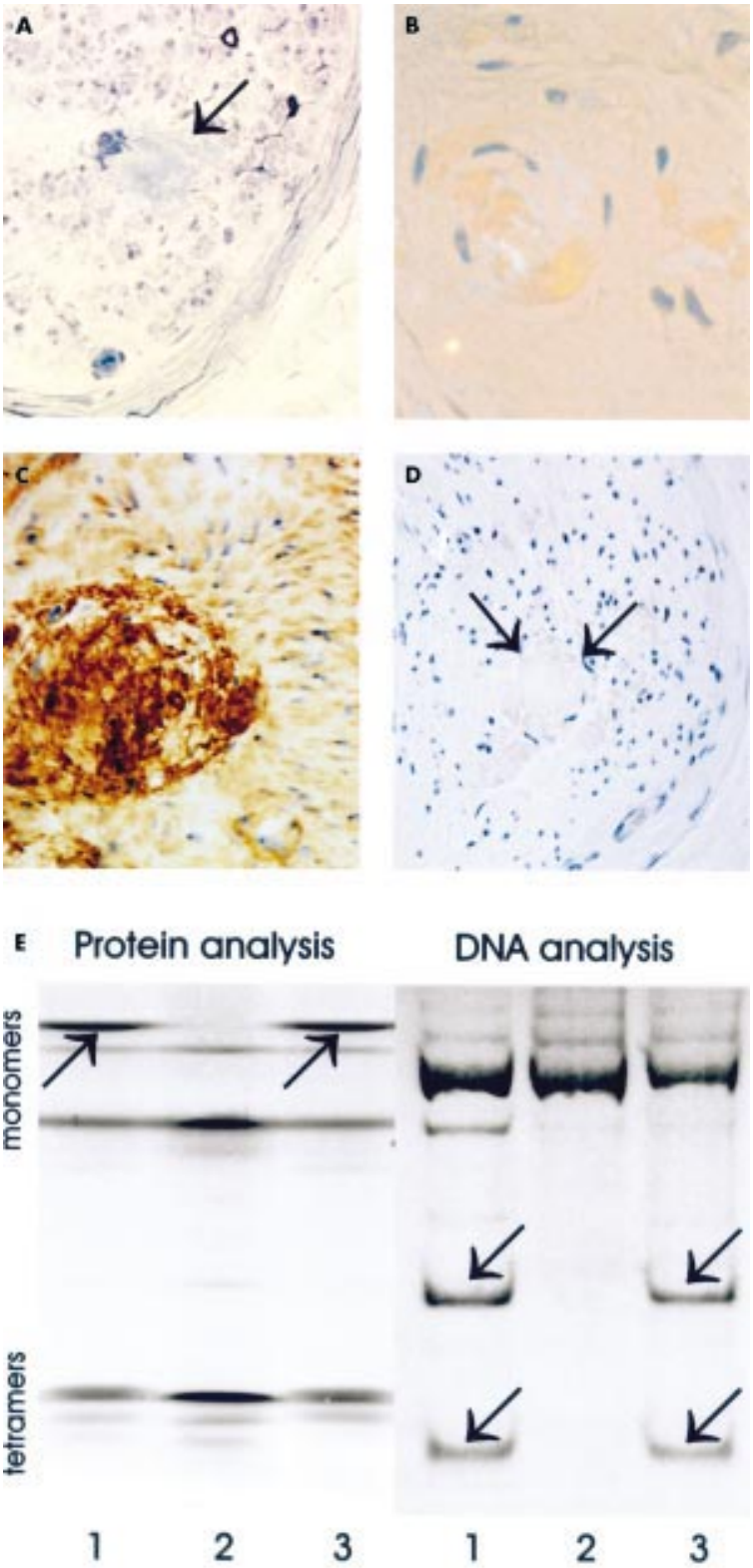

Figure 1 (A) Semithin section of sural nerve stained with methylene blue azure-two, showing massive loss of myelinated fibres and an amyloid plaque (arrow). (B) Paraffin section with Congo red staining showing birefringence in polarised light. (C) Cryosection reacted with antibodies to transthyretin (prealbumin Dako, 1:20 000), showing dense immunoreactivity of the plaque for transthyretin. (D) Cryosection reacted with polyclonal antibodies to human IgG (Dako, 1:1000) showing no immunoreaction on the amyloid plaque (arrows). (E) Protein analysis by hybrid isoelectric focusing under half denaturing conditions[1] (left), and restriction fragment analysis after amplification of exon 2 of the transthyretin (TTR) gene and digestion with Nsi I for the identification of the ATTR(Val30Met) mutation (right). Lane 1 represents the patterns of the patient, lane 2 the patterns of a normal control individual, and lane 3 the patterns of a known FAP patient with normal TTR and the ATTR(Val30Met) mutation.

lymphoid B cells of low proliferative activity and no clear birefringence in Congo red staining. A diagnosis of smouldering B cell lymphocytic leukaemia (B-CLL) was made.

Sural nerve biopsy disclosed a dramatic loss of both myelinated and unmyelinated fibres without signs of regeneration (fig 1A). Surprisingly, several amyloid plaques were seen on Congo red staining (fig 1B). Immunohistochemistry showed unequivocal immunoreactivity for transthyretin (TTR) (fig 1C), while polyclonal antibodies to human IgG (fig 1D) stained negative. On skin biopsy of the left lower leg, there was total loss of epidermal nerve fibres. Protein and DNA analysis showed heterozygosity for normal TTR and the amyloidogenic mutation ATTR(Val30Met) (fig 1E) leading to the diagnosis of familial amyloidotic polyneuropathy (FAP).

This patient presents a chance association of B-CLL with "sporadic" FAP. Several cases of a B-CLL associated chronic sensorimotor neuropathy, either caused by neoplastic nerve infiltration or as a paraneoplastic condition, have been described.[2] The initial tentative diagnosis of CLL associated neuropathy was revised when amyloid plaques immunoreactive for TTR were found in the sural nerve biopsy and the ATTR(Val30Met) mutation was demonstrated.

In most cases FAP is caused by a point mutation in the TTR gene. About 80 different mutations of the TTR gene have been identified, the Val30Met mutation being by far the most common. In Europe, this mutation clusters in distinct areas of Portugal and Sweden. Smaller foci or single families/cases have been described in most other European countries. In Germany about half the known FAP patients are carriers of the ATTR(Val30Met) mutation. Age of onset and penetrance of ATTR(Val30Met) amyloidosis vary considerably. While Portuguese patients from the focus Povoa do Varzim/Vila do Conde develop the disease at a mean age of 31 years, the age of onset among Swedish patients is approximately 57 years. Penetrance is high and progression is rapid in Portugal, but penetrance is low and progression slow in Sweden.[3 4] Additional genetic and environmental factors probably influence the wide range of both age at onset and severity of FAP.

Most FAP patients present with fibre length dependent sensorimotor and autonomic neuropathy. Cardiac involvement, as observed in our patient, is less common and seen in cases of severe polyneuropathy only. Renal involvement is much less prevalent in FAP than in AL amyloidosis, and macroglossia does not occur in FAP. Differentiation of amyloid in tissues by immunohistochemistry is essential for identifying the major amyloidogenic protein. Finally, the diagnosis of FAP must be based on molecular protein/DNA analysis.

Although FAP is a disease of autosomal dominant inheritance, a negative family history of polyneuropathy or amyloidosis does not rule out the disease, owing to incomplete penetrance or a new mutation. FAP should be considered in *all* cases of sporadic neuropathy with prominent autonomic symptoms, trophic ulcers, or weight loss, even in countries with a low incidence like Germany. Possibly the prevalence of FAP is underestimated in such countries because of incomplete diagnostic workup.

The recognition of FAP is important for two main reasons. First, treatment is possible by liver transplantation when performed early in the course of disease.[5] Second, diagnosis of FAP in the propositus is essential for identifying relatives at risk for the disease and for providing adequate genetic counselling.

M Buttmann, M Marziniak, K V Toyka, C Sommer
Neurologische Klinik und Poliklinik, Julius-Maximilians-Universität, Josef-SchneiderStr 11, 97080 Würzburg, Germany

K Altland
Institut für Humangenetik, Justus-Liebig-Universität, Schlangenzahl 14, 35392 Gießen, Germany

Correspondence to: Dr Claudia Sommer; sommer@mail.uni-wuerzburg.de

References

1 **Jenne DE**, Denzel K, Blätzinger P, *et al*. A new isoleucine substitution of Val-20 in transthyretin tetramers selectively impairs dimer-dimer contacts and causes systemic amyloidosis. *Proc Natl Acad Sci USA* 1996;**93**:6302–7.
2 **Creange A**, Theodorou I, Sabourin JC, *et al*. Inflammatory neuromuscular disorders associated with chronic lymphoid leukemia: evidence for clonal B cells within muscle and nerve. *J Neurol Sci* 1996;**137**:35–41.
3 **Sousa A**, Coelho T, Barros J, *et al*. Genetic epidemiology of familial amyloidotic polyneuropathy (FAP)-type I in Povoa do Varzim and Vila do Conde (north of Portugal). *Am J Med Genet* 1995;**60**:512–21.
4 **Sousa A**, Andersson R, Drugge U, *et al*. Familial amyloidotic polyneuropathy in Sweden: geographical distribution, age of onset, and prevalence. *Hum Hered* 1993;**43**:288–94.
5 **Adams D**, Samuel D, Goulon-Goeau C, *et al*. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. *Brain* 2000;**123**:1495–504.

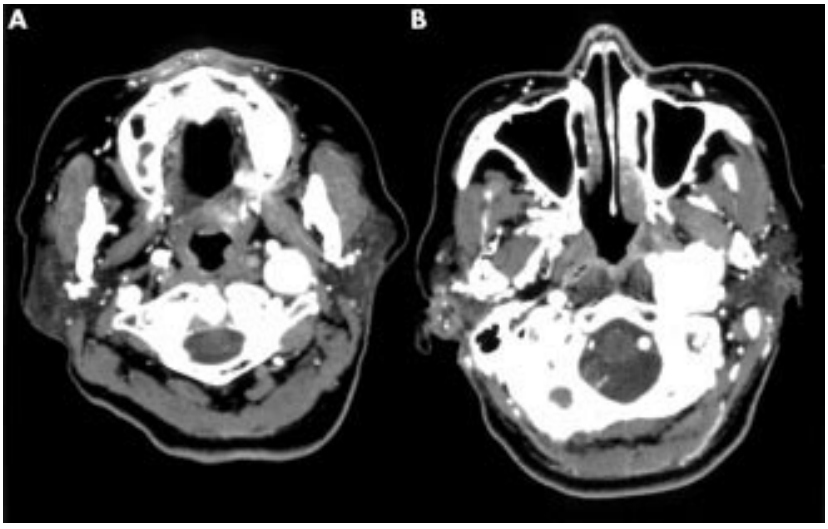

Figure 1 Contrasted axial computed tomography scan (A) at the level of the atlas and (B) through the base of the skull. There was a large aneurysm of the extracranial internal carotid artery.

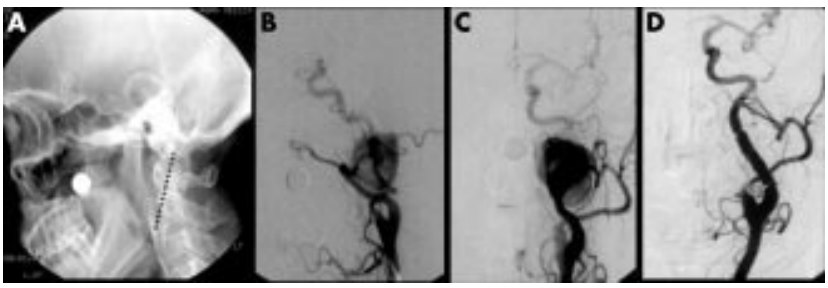

Figure 2 (A) Blaisdell line (dashed oblique line) between the angle of the mandible and the tip of the mastoid process. (B,C) Anteroposterior and lateral view of left carotid angiography showing an aneurysm on the extracranial internal carotid artery. It started near the Blaisdell line and ended at the base of the skull. (D) Postoperative angiography showing the patent venous graft.

Aneurysm of the extracranial internal carotid artery presenting as the syndrome of glossopharyngeal pain and syncope

The syndrome of glossopharyngeal pain and/or syncope mimicking idiopathic glossopharyngeal neuralgia has been reported to be associated with a variety of intracranial or extracranial conditions[1] including mass lesions in the parapharyngeal space,[2 3] the elongated styloid process,[4] and multiple sclerosis.[5] However, aneurysm of the cervical portion of the internal carotid artery (ICA) presenting as episodic glossopharyngeal pain and syncope has not been reported previously to the best of our knowledge. We report here the first such case that was successfully treated by surgical resection of the aneurysm.

A 66 year old woman with a two year history of paroxysmal attacks of pharyngeal pain with occasional syncopal episodes was admitted to our hospital. She had been in good health until two years previously, when she first noticed pain in the region of the left