Transthyretin Leu12Pro is associated with systemic, neuropathic and leptomeningeal amyloidosis

M. Brett, M. R. Persey, M. M. Reilly, T. Revesz, D. R. Booth, S. E. Booth, P. N. Hawkins, M. B. Pepys and J. A. Morgan-Hughes

Address for correspondence:

Dr Matthew Brett
MRC Cyclotron Unit
Hammersmith Hospital
Du Cane road
London W12 0HS
Tel: 0181 383 3162
Fax: 0181 383 2029

Running title:

TTR Leu12Pro and leptomeningeal amyloid

Summary

We report a middle aged woman with a novel transthyretin (TTR) variant, Leu12Pro. She had extensive amyloid deposition in the leptomeninges and liver as well as the involvement of heart and peripheral nervous system which characterises familial amyloid polyneuropathy (FAP) caused by variant TTR. Clinical features attributed to leptomeningeal amyloid included radiculopathy, central hypoventilation, recurrent subarachnoid haemorrhage, depression, seizures and periods of decreased consciousness. MRI showed marked enhancement throughout her meninges and ependyma, and TTR amyloid deposition was confirmed by meningeal biopsy. The simultaneous presence of extensive visceral amyloid and clinically significant deposits affecting both the peripheral and central nervous system extends the spectrum of amyloid related disease associated with TTR mutations. The unusual association of severe peripheral neuropathy with symptoms of leptomeningeal indicates that leptomeningeal amyloidosis should be considered part of the syndrome of TTR related FAP.

Keywords

Familial Amyloid Polyneuropathy - Oculoleptomeningeal amyloidosis - Transthyretin

Introduction

Familial amyloid polyneuropathy (FAP) is the most common form of hereditary systemic amyloidosis. It is an autosomal dominant condition, usually caused by mutation in the gene for plasma transthyretin (TTR), although a few kindreds are known with a similar phenotype caused by apolipoprotein AI gene mutations. Typical features of TTR-related FAP include severe peripheral and autonomic neuropathy and variable but usually modest amyloid involvement of the spleen, kidneys, heart, eyes, adrenals and thyroid gland. Hereditary oculoleptomeningeal amyloidosis (OLMA) is a rare syndrome in which there are opacities of the vitreous humor and CNS symptoms associated with leptomeningeal amyloidosis. OLMA is less well characterised than FAP, but may also be associated with TTR mutations (Goren *et*

al., 1980; Herrick *et al*., 1996; Petersen *et al*., 1995; Uitti *et al*., 1988; Vidal *et al*., 1996). In this article we report an English patient with a novel TTR mutation who had classical features of FAP in addition to those of OLMA. She also had unprecedentedly severe systemic amyloidosis, including amyloid deposition in the liver. Although more than 95% of circulating TTR is produced by the liver, significant parenchymal amyloid deposition has not been reported affecting the liver in patients with amyloidogenic TTR mutations. Her phenotype supports the idea that there is a continuum of pathology associated with amyloidogenic TTR mutations and her major system involvement further extends the spectrum of amyloid disease that may occur in this setting.

Case report

Our index case was 38 years old when she first began to notice easy bruising. Five years later, in 1985, she began to get persistent headaches, and six months after this presented with severe headache of sudden onset. CT and lumbar puncture confirmed subarachnoid blood, but her angiogram showed no definite bleeding point, and she was managed conservatively. Two months later she had another subarachnoid bleed, but her angiogram was unchanged. She remained well after discharge until 1990, when she started to notice hearing loss in both ears, increasingly severe headaches, unsteadiness, urinary frequency, incomplete bladder emptying and poor urinary stream. CT scan of her brain showed hydrocephalus, and insertion of a right lateral ventriculoperitoneal shunt was complicated by a small subdural haematoma and slow recovery from anaesthesia. After the shunt, her unsteadiness and urinary symptoms partially improved, but she began to notice a dry mouth, dry eyes, constipation, and orthopnoea.

In 1992 she became increasingly nauseated and unsteady when walking, and by the middle of 1993 she noticed weakness and numbness in her feet. CT scan showed a contracted lateral ventricle on the shunted right side, but the rest of her ventricular system was dilated. She received a left lateral ventricular shunt, again complicated by some bleeding. Her ventricular CSF had a raised protein of 1.1 grams per litre (g/L); CSF protein from her earlier lumbar punctures had been normal. After the operation she deveolped urinary retention and had to be catheterised for a few days.

There was little improvement of her symptoms after the second shunt. At the end of 1993 she started to get floaters in both eyes and in May 1994, at the age of 51, she was admitted after several weeks of headaches and intermittent confusion. She had patchy sensory loss in the feet, marked ataxia of gait, and was in painless urinary retention. CT showed no hydrocephalus, and chest X-ray showed cardiomegaly with pleural effusions. Her ECG had anterior Q waves with lateral T wave inversion, and echocardiogram showed a thickened septum and posterior wall, both typical of cardiac amyloid (Staunton, 1991). Several lumbar punctures over the course of her admission found CSF protein values between 4 and 19 g/l, whereas ventricular CSF drawn from her shunt reservoirs had protein values of 1.1 -1.4 g/l, suggesting an element of spinal CSF block. An enhanced MRI scan showed striking enhancement of both cerebral and spinal meninges (see figures 1 and 2).

(Figures 1 and 2 near here)

In June of 1994 she had a right sided focal seizure with altered consciousness, and some left temporal EEG changes. Later that month she had a posterior fossa meningeal biopsy. After the operation she remained intermittently confused and drowsy for nine days, and blood gases showed her to be in variable type 2 respiratory failure. Two days after her operation she had episodes of alternating apnoea and hyperventilation which gradually resolved over the following week.

Histology of the meningeal specimen showed extensive leptomeningeal amyloid (see results). She later went on to have a vitrectomy which also showed amyloid on staining with Congo Red. Immunohistochemistry of the meningeal amyloid deposits demonstrated transthyretin, and direct DNA sequencing revealed a mutation in the transthyretin gene.

On examination she had markedly dry eyes and mouth, and several areas of bruising. She had postural hypotension, with a lying blood pressure of 90/50 dropping to 50/30 on standing. There were signs of moderate biventricular cardiac failure. She was alert and orientated; both her fundi were partially obscured by vitreous debris and her pupils did not react to light, but responded slowly to accommodation. She had moderate bilateral sensorineural hearing loss and slow tongue movements.

Tone was normal but there was distal wasting and weakness. Coordination was slightly impaired in her arms, but she had a markedly ataxic gait. Her reflexes were sluggish throughout, and ankle jerks were only present with reinforcement; both plantar responses were flexor. There was patchy loss of light touch and pinprick in a glove and stocking distribution, with moderate reduction of temperature sensation. Joint position sense was reduced in her hands, and in her feet up to her knees. Formal psychometry revealed an average IQ, which represented a fall from her estimated premorbid level.

Nerve conduction studies (NCS) demonstrated reduced amplitude sensory action potentials (SAPs) in the hands, and absent SAPs in the sural nerves. Conduction velocities were normal and there was evidence of distal denervation on electromyography (EMG). Paraspinal and intercostal EMG showed some fibrillation, increased insertional activity and complex repetitive discharges in all muscles sampled. The overall picture was therefore of an axonal sensorimotor neuropathy combined with a diffuse radiculopathy. Autonomic function tests confirmed postural hypotension, and blocked heart rate response to cold, mental arithmetic and Valsalva manoeuvre.

She suffered severe night time hypoxia, and continuous monitoring of her oxygen saturation showed prolonged cycles of hypoxia with saturations as low as 40%, suggesting that there was a significant central component to her reduced ventilation.

In January 1995 she became very depressed. Later that month, she became increasingly drowsy and hypoxic. The reason for the confusion was not clear; blood gas results were adequate on continuous inhaled oxygen, repeat CT scan showed no hydrocephalus, and biochemistry was unremarkable. Mineralocorticoid treatment had been started, and supine blood pressure was adequate at 130/100, although she still had severe symptomatic postural hypotension. She continued to be troubled by dyspepsia, constipation and nausea. The prognosis was clearly very poor, and after full discussion the family declined to consider liver transplantation, and decided that she should have no further active treatment or investigation. However, she did not deteriorate, and in April 1995 she began to become less confused. This seemed to fluctuate from day to day. When she was coherent she continued to be severely depressed. In April she had a second partial seizure. By the end of June, her mental state had improved and she was consistently alert and oriented. In July 1995 she was discharged, and died at home 5 months later at the age of 53 years. There was no post mortem.

Family history revealed that the patient's mother had committed suicide at the age of 62 after two years of depression and physical illness, including minor urinary symptoms, constipation and falls. She had been admitted at the age of 61 with severe abdominal pain, and while in hospital had two episodes of unexplained confusion, and complained of flashing lights and spots in front of her eyes, although neurological and ophthalmological examination were recorded as normal. A year later she was admitted to the local psychiatric hospital with severe depression, and committed suicide a few months later. The post mortem report has been lost but tissue blocks preserved from her heart, lung and kidney were obtained for study (see below). There was no other family history of psychiatric or neurological disease. The family were unwilling for us to examine or investigate other family members, and declined genetic counseling.

Methods

Histology

Amyloid was identified by green birefringence using sections stained with Congo Red viewed in polarised light (Puchtler *et al*., 1962). TTR immunoreactivity was sought as previously described (Booth *et al*., 1995b). Sections were similarly stained using antisera to immunoglobin light chains and serum amyloid A protein.

Serum amyloid P component scintigraphy

Whole body scintigraphy following administration of ^{123}I-labelled serum amyloid P component was performed as previously described (Hawkins *et al*., 1990; Hawkins *et al*., 1988). Approximately 150 MBq of ^{123}I-SAP was injected and anterior and posterior whole body images were obtained at 24 hours.

Sequencing of TTR gene

DNA was extracted from whole blood and the four exons of the entire TTR gene amplified by PCR using *taq* polymerase as previously described (Booth *et al*., 1995b). Aliquots of 100µl of the PCR products were purified by size fractionation on an agarose gel and the bands subsequently discovered were used

for the sequencing reaction for each primer. A reaction mixture containing 2µl of primer, 2µl of sequencing buffer and 6µl of template was boiled for 2 minutes, frozen in a dry ice methanol bath and 5µl of Mastermix was added. Just after thawing, 3µl of the mixture was added to 2.5µl of each of the four dideoxynucleotides before incubating the termination reaction at 37°C for 2 minutes, and finally adding 4µl of stop solution. The same primers were used for PCR and sequencing except for exon 4 where a different primer gave a better sequence.

Results

Histology

A posterior fossa meningeal biopsy provided membranous fragments of grey tissue measuring 0.7cm across. Most of the specimen was composed of rather paucicellular tissue with dense parallel collagen bundles suggestive of an origin in dura mater, and separate fragments of thickened leptomeninges were also present. Moderate amounts of acellular, eosinophilic material were deposited around dural blood vessels and much more abundantly in the leptomeninges (figure 3), and this was confirmed as amyloid by Congo Red staining.

(Figure 3 near here)

There was specific staining of the deposits with the anti-TTR serum which was abolished by prior absorption with TTR. There was no specific staining with the antisera to light chains or serum amyloid A protein. No amyloid was detected in sections of heart, lung and kidney from the mother's post mortem.

Serum amyloid P component scintigraphy

Serum amyloid P component scintigraphy showed quite intense abnormal uptake of tracer in the liver, spleen and kidneys indicating the presence of substantial amyloid deposits in these sites. Liver amyloid

has not been demonstrated by this method in any of the more than 60 patients with other amyloidogenic TTR mutations who have been studied in the Immunological Medicine Unit at Hammersmith Hospital.

Gene sequencing

Amplification and direct sequencing of all four exons of the TTR gene showed that our patient was heterozygous for a single base change in one allele of exon 2, altering the codon for residue 12 of the native protein from Leu (CTG) to Pro (CCG). The remainder of the sequence was normal.

Discussion

More than 60 variant forms of TTR have now been identified, over 80% of which are associated with hereditary amyloidosis (Benson and Uemichi, 1996). Although some such mutations present predominantly with cardiac amyloidosis, FAP is by far the most common syndrome associated with variant TTR.

The clinical picture of FAP was first described by De Bruyn and Stern (1929), although they misdiagnosed their case as Déjerine-Sottas disease (De Navasquez and Treble, 1938). Andrade (1952) accelerated the study of the disease with his classic description of cases in the Oporto region of Portugal. It was subsequently shown that Andrade's patients had a variant TTR (Costa *et al*., 1978) with a methionine for valine substitution at position 30 in the mature protein (Dwulet and Benson, 1983). Since then many different mutations of TTR have been associated with FAP (Benson and Uemichi, 1996).

Staunton (1991) and Reilly (Reilly and King, 1993) have recently reviewed the clinical aspects of TTR related FAP. The age of onset varies between families, from the third decade (Andrade, 1952; Silva Horta *et al*., 1964) to the sixth (Staunton *et al*., 1987). By definition all kindreds with FAP suffer from peripheral neuropathy, which is an axonal sensorimotor polyneuropathy (Staunton *et al*., 1987; Thomas and King, 1974), and usually begins in the feet. Some families develop early carpal tunnel syndrome (Rukavina *et al*., 1956). Autonomic dysfunction is common and presents with impotence,

gastrointestinal symptoms or postural hypotension. There is often amyloid cardiomyopathy, which may cause heart failure and rhythm disturbances. Some families suffer from vitreous opacities (Gorevic and Rodrigues, 1994). Amyloid nephropathy is sometimes prominent.

There are two other proteins that are known to be associated with FAP. Variant gelsolin causes lattice corneal dystrophy and cranial neuropathy, followed by peripheral neuropathy (Maury *et al*., 1990; Meretoja, 1969). Mutations in apolipoprotein AI are sometimes associated with polyneuropathy similar to that of TTR-related FAP, although most affected patients have very extensive systemic amyloidosis involving many organ systems (Nichols *et al*., 1990; Van Allen *et al*., 1969).

Until recently it was thought that CNS symptoms were not a major feature of TTR-related amyloidosis. However, it has recently become clear that the syndrome of OLMA is associated with TTR mutations. Goren and others (1980) were the first to use the term oculoleptomeningeal amyloidosis to describe a syndrome of familial systemic amyloid that caused symptoms by involving the vitreous humour and the leptomeninges. Apart from Goren's report, there are now five other families in the literature which fit this description.

Hamburg reported the first cases (1971). He described two brothers with vitreous opacities and muscle wasting who died in their sixth decade. One had a spinal cord lesion that was attributed to arachnoiditis; a year later he became disorientated and suffered attacks of vomiting, and died the following year. His brother was ataxic and hyperreflexic at presentation, and two years later required admission with convulsions, vomiting, and drowsiness; he too died after a year of progressive decline. Okayama and others (1978) reported the cases of a mother and seven children with vitreous opacities and evidence of an autonomic neuropathy. Three of the cases also had CNS symptoms: one had died of a convulsion age 45 years and another had died in a state of chronic 'delirium' aged 39. Their index case presented with vitreous opacities, but gradually became demented. He had episodes of confusion and loss of consciousness lasting several hours which were sometimes associated with transient aphasia or right hemiparesis. Electrophysiology showed a mild peripheral neuropathy. He died age 40 after a left focal seizure. There was some inconclusive biochemical evidence for TTR amyloid in these patients (Kitomoto *et al*., 1986).

Goren and his colleagues (1980) described an American / German family with a similar clinical picture. Six patients in this family had died in their sixth decade with a history of progressive dementia, transient

stroke-like episodes with altered consciousness, headaches, convulsions and visual loss from vitreous opacities. Two patients had signs of peripheral neuropathy. Recent genetic analysis found a variant TTR in the affected family members, with a glycine for valine substitution at residue 30 of the TTR protein (Petersen *et al*., 1995). Uitti and others (1988) reported three cases from an Italian family. Their index case presented with headaches followed by urinary symptoms, hearing and visual loss, right sided numbness, difficulty in walking and dementia. Examination showed dysarthria, a spastic paraparesis and ataxia; he deteriorated with increasing dementia and quadriparesis, and died of respiratory failure. His sister had headaches, sensory symptoms in her legs and arms, urinary symptoms and hyperreflexia. She went on to develop facial weakness, nystagmus, progressive memory loss and aphasia. Her son had had convulsions, headaches, psychosis, and episodes of altered consciousness with hemiparesis of left or right side. He suffered a frontal haematoma age 28. After this was evacuated he had cycles of fluctuating awareness and died a year later. The authors reported an abnormal transthyretin in the blood of one of their patients.

In the last two years there have been two further reports of cases of OLMA. Vidal and others (1996) give brief clinical and pathological details of a family with four affected members, and note memory loss, episodic confusion, cerebellar and pyramidal signs, and hearing loss. Affected members had a glycine for aspartate substitution at residue 18 of TTR. Finally Herrick and others (1996) have reported the case of a Mexican woman with extensive amyloid of the leptomeninges demonstrated on biopsy. She had a past history of 'spinal meningitis' and a transient stroke-like episode, and presented at age 69 with a history of slowly progressive fluctuating confusion, weakness and sensory loss in the legs, and incontinence of urine and stool. Genetic analysis revealed a variant TTR with a methionine substitution at residue 30.

In each but the last of these reports there were post mortem findings from one or more of the affected patients. They all showed systemic amyloidosis, with variable degrees of peripheral nerve involvement. The characteristic finding was of extensive amyloid thickening of the leptomeninges and subarachnoid vessels. Amyloid in the blood vessels disappeared as the vessels penetrated the parenchyma. Most cases had a moderate degree of hydrocephalus, and in most the ependyma of the ventricles had a covering of amyloid deposits. There was diffuse neuronal loss in the CNS parenchyma which was most

severe in the superficial layers, and evidence of subpial gliosis in the white matter. Some patients had superficial infarcts of the cerebral and cerebellar cortex.

Our patient had the characteristic clinical features of TTR related FAP. She had an ascending axonal sensorimotor polyneuropathy and severe autonomic dysfunction, with urinary symptoms, constipation, sicca syndrome, postural hypotension and tonic pupils. She had amyloid vitreous opacities, mild renal impairment, and cardiac failure, with typical ECG and echocardiogram findings for amyloid cardiomyopathy (Staunton, 1991). She also had many clinical features that are not part of the TTR FAP syndrome, but are suggestive of OLMA. Thus she had recurrent subarachnoid haemorrhage, a high CSF protein, hydrocephalus, radiculopathy, reduced respiratory drive, episodic reduction in conscious level, fluctuating confusion and severe depression. A meningeal biopsy confirmed that she had extensive amyloid deposits in her meningeal vessels and within the dura and MRI scan showed very widespread meningeal enhancement. The MRI and biopsy findings suggest that she had similar meningeal pathology to that in patients with OLMA. However, some features of our case are unusual for both syndromes, and merit further comment.

Our patient is the first reported with recurrent subarachnoid haemorrhage (SAH) attributed to leptomeningeal amyloid. Although this feature is almost unique to our patient, it is well known that blood vessels infiltrated by amyloid are likely to bleed in amyloid angiopathy associated with both Cystatin C4 and Aß amyloidosis. There is also some evidence for this in previous reports of OLMA. Among Uitti's cases (Uitti *et al*., 1988) one patient had a large frontal intracerebral bleed, and another had an old occipital haematoma at autopsy. Koeppen and others (1985; 1990) reported that a patient with TTR related FAP had died from a SAH age 43. A Japanese patient with FAP died of a SAH (Ikeda *et al*., 1987), but this was ascribed to a thoracic arteriovenous malformation found at post mortem. Lastly, Arpa Gutierrez and others (1993) described a patient with TTR related FAP who had had a pontine haemorrhage in her fifth decade. At post mortem, she had extensive leptomeningeal amyloid, and amyloid in the vessels around the haemorrhage.

Episodes of impaired consciousness were a prominent symptom in our patient, as in previous cases of OLMA. No convincing explanation has yet been offered for this phenomenon. In past reports, these episodes may last from hours to many days, and they are often associated with focal signs suggesting cortex or brainstem involvement (Goren *et al*., 1980; Hamburg, 1971; Krücke, 1950; Okayama *et al*., 1978;

Uitti *et al*., 1988). Our patient was admitted with a complaint of intermittent confusion, and had two significant periods of drowsiness and confusion while in hospital. These were not fully explained by her respiratory failure. Goren et al (1980) suggested that such episodes in their patients might have been due to intermittent hydrocephalus, although they found no evidence in life that this was the case. Observations in our patient do not support this mechanism, because she suffered similar episodes when she had two functioning ventriculoperitoneal shunts. It is also unusual for hydrocephalus to cause the focal deficits that occur in OLMA such as alternating hemiparesis or aphasia (Goren *et al*., 1980; Okayama *et al*., 1978; Uitti *et al*., 1988). It is possible that these represent transient episodes of ischaemia of cortex and brainstem. In our patient we postulate that the respiratory failure and reduced level of consciousness were both due to episodes of brainstem ischaemia. Post mortem findings in patients with OLMA often show narrowing and occlusion of cerebral blood vessels, with some recanalisation (Goren *et al*., 1980). It is possible that this vessel narrowing coupled with reduced autoregulation by the amyloid-laden vasculature may lead to prolonged ischaemia without infarction.

Our patient had radiculopathy as well as moderate axonal neuropathy, and there is some evidence for radiculopathy in other patients with OLMA. Uitti (1988) reported paraspinal muscle atrophy in their index case, and Goren and others (Goren *et al*., 1980) reported L5 radiculopathy in one of their patients. Radiculopathy can be difficult to detect both clinically and by electrophysiology when there is also a peripheral neuropathy. For that reason we looked at paraspinal muscle EMG, and there were denervation changes. It is interesting that several authors have commented that there is little relationship in FAP between the severity of neuropathy and the amount of amyloid in peripheral nerves (Staunton, 1991). Some post mortem studies in FAP have shown extensive disruption of the dorsal root ganglia and motor roots (De Navasquez and Treble, 1938; Juliao *et al*., 1974; Takahashi *et al*., 1991), and this may be a major factor in the dying-back neuropathy (Staunton, 1991; Thomas and King, 1974).

Lastly, our patient had striking findings on imaging. The enhanced MRI scan of her brain and spinal cord was very unusual, with profuse and widespread enhancement of the meninges. Such enhancement may not be surprising given the widespread amyloid deposits in meninges and blood vessels described in post mortem studies of OLMA. Herrick and others (1996) have recently reported similar MRI findings in their patient with symptoms of OLMA. It therefore seems likely that this picture is characteristic of leptomeningeal amyloidosis. The radiolabelled serum amyloid P component scan appearances were also

unusual; not only were the amyloid deposits more extensive that is usually seen, but hepatic amyloid deposits have not previously been identified by these means in patients with TTR mutations (Hawkins, 1994; Hawkins *et al*., 1996) or found within the liver substance in histological studies. Although the liver is the most important site of TTR synthesis, there are presumably factors within the microenvironment of the hepatic parenchyma that do not favour amyloid fibril formation. The extensive nature of our patient's systemic amyloid deposits, including the liver involvement, may simply reflect the extremely prolonged course of her disease, which may also be an important factor in the development of her CNS features.

Our patient differs from previous cases of OLMA in that she had prominent autonomic and peripheral neuropathy. She therefore has a phenotype that is intermediate between typical TTR-related FAP and OLMA. This suggests that leptomeningeal amyloid may not be a distinct clinical entity, but part of a spectrum of TTR disease. There are three lines of evidence to support this conclusion. Firstly, there are a few other patients in the literature with classical FAP and symptoms of leptomeningeal disease. Secondly, the post mortem findings from patients with classical FAP often show severe leptomeningeal amyloid (Benson, 1996). Lastly, one patient with symptoms of OLMA has a TTR mutation which is commonly associated with classical TTR FAP (Herrick *et al*., 1996).

There are sporadic reports of patients with classical FAP and CNS disease. The first was probably that of Götze and Krücke (1942; Krücke, 1950, case 1). They described a sculptor with a family history of renal disease who suffered symptoms of a progressive autonomic and peripheral neuropathy. They comment on his marked affective change. His conversation became facile, his memory was impaired, and he was unable to keep track of events in the news, although he was living in the Germany of 1939. Later, Krücke (1950, case 2) reported another patient with an autonomic and sensory neuropathy and evidence of a cardiomyopathy. She also had headaches, and after a lumbar puncture, developed severe meningism and became increasingly drowsy and unconscious over five days. Ventricular puncture showed no increase in CSF pressure and she gradually recovered. She died a year later after a series of focal seizures. Autopsy of both patients showed severe leptomeningeal amyloid with superficial cortical atrophy and infarcts. Kantarjian and DeJong (1954) described the cases of a father and two daughters with peripheral and autonomic neuropathy and vitreous opacities. Both the daughters suffered marked agitation and depression and had a high CSF protein. A limited post mortem on the

father found systemic amyloid and fibrosis of the spinal cord, although there is no comment on the brain or leptomeninges. There are other reports of patients with FAP and early strokes (Arpa Gutierrez *et al*., 1993; Ikeda *et al*., 1987, case II-5 of family T).

The large majority of cases of TTR related FAP have no CNS symptoms, but post mortems often show severe leptomeningeal amyloid. Thus, Portuguese patients with classical FAP had amyloid deposits in the meninges of the cerebral hemispheres and spinal cord, as well as the ependyma and choroid plexus (Silva Horta *et al*., 1964). The authors comment that these deposits were more marked than in any other generalised amyloidosis. Autopsy of Brazilian (Juliao *et al*., 1974) and Japanese patients (Takahashi *et al*., 1991; Ushiyama *et al*., 1991) with TTR related FAP found amyloid of the vessels of the meninges and to a lesser extent in the connective tissue. Benson and Cohen (1977) reported a family of Swedish origin with FAP. At post mortem they found extensive amyloid of the leptomeninges, but also deposits of amyloid in the superficial layers of cerebral cortex and within the brain stem and spinal cord. Arpa Gutierrez found severe leptomeningeal amyloid in a case of FAP with a pontine haemorrhage (1993).

Herrick et al (1996) have recently reported a patient with OLMA and TTR Met 30. TTR Met 30 is the most common variant associated with FAP, and is the cause of disease in the families that Andrade originally described. It is therefore very unlikely that OLMA is genetically distinct from FAP. Indeed leptomeningeal amyloidosis may not be specific to TTR. Van Allen (1969) reported patients with apolipoprotein AI amyloid who had hearing loss and ataxia. One of his cases had arachnoid adhesions at laminectomy, and died of intracerebral haemorrhage age 46. Post mortem studies on his patients showed moderate amyloid in the meninges, with severe amyloid of dorsal ganglia and spinal roots. CNS symptoms are uncommon in gelsolin FAP (Boysen *et al*., 1979; Meretoja, 1969; Sunada *et al*., 1993), but Meretoja and Teppo (1971) report one patient with ataxia and an upgoing plantar who died of an intracerebral haemorrhage. Post mortem of their three patients again showed moderate leptomeningeal amyloid.

Our patient has a new TTR mutation and an unusual phenotype. The relation between them is not clear. However, it is possible that specific mutations of TTR may be more likely to cause leptomeningeal amyloidosis. Proline substitution at position 55 in the TTR molecule is associated not only with very aggressive disease *in vivo* (Jacobson *et al*., 1992), but also significant loss of TTR tetramer stability *in vitro*, promoting denaturation to a putative amyloidogenic intermediate and thus increasing

amyloidogenicity (McCutchen *et al*., 1993; McCutchen *et al*., 1995). The apparent amyloid-promoting feature of this proline substitution may relate to its ability to destabilise β strands (Wood *et al*., 1995), which are a prominent feature of wild-type TTR. This effect may also result from the creation of a proline-proline doublet at positions 11-12, as predicted by the DNA sequence for the variant reported here. Finally, it is of interest that Pro 12 represents the third mutation in the TTR gene which causes changes in the A strand of the mature protein (Booth *et al*., 1995a; Vidal *et al*., 1996), a region in which amino acid substitutions were previously considered unlikely to have a significant influence on the stability of the protein.

Figure 1

Gadolinium enhanced T1 weighted MRI of cervical and thoracic spinal cord. There was marked multinodular enhancement over the surface of the spinal cord throughout its length.

Figure 2

Gadolinium enhanced T1 weighted MRI of brain. There was extensive enhancement from the surface of the brain, and of the fourth and lateral ventricles.

Figure 3

Photomicrograph showing thickened leptomeninges with amyloid deposits (arrows). Heamatoxylin and eosin x 200.

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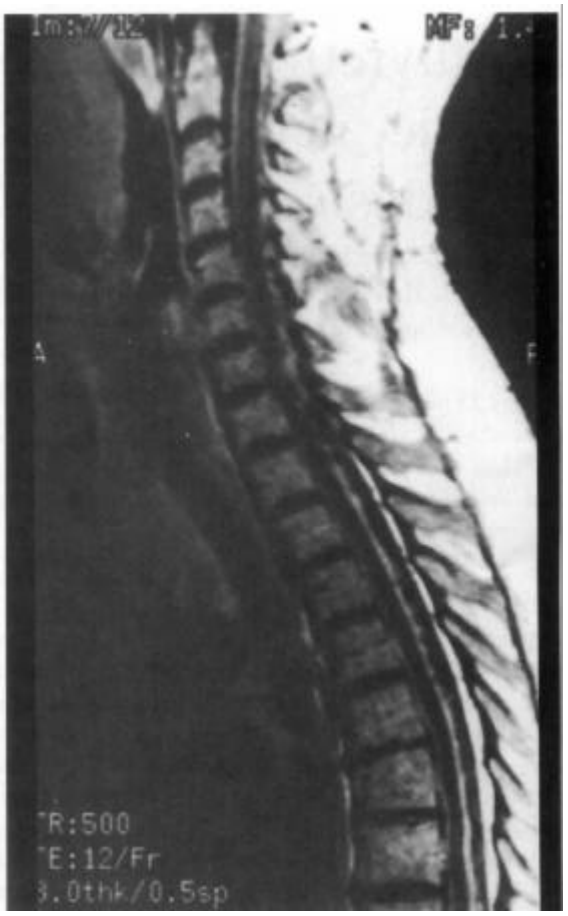
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