SHORT REPORT

A novel amyloidogenic transthyretin variant, Gly53Ala, associated with intermittent headaches and ataxia

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We report a novel transthyretin variant, Gly53Ala, in a 44-year-old British woman who presented with severe episodic headaches, often with focal neurological deficit, before developing progressive ataxia, depression, dementia and eventually peripheral neuropathy. Transthyretin amyloidosis was confirmed on biopsy of the heart muscle. Serum amyloid P component scintigraphy did not show visceral amyloid in extra-cardiac sites, but magnetic resonance imaging indicated diffuse leptomeningeal amyloidosis.

Familial amyloid polyneuropathy (FAP) is an autosomal dominant disorder caused by defects in the transthyretin (TTR) gene that encodes four exons producing a protein of 127 amino acid subunits. Worldwide, FAP is most commonly associated with the mutation that encodes substitution of valine by methionine at position 30 (Met30), although >80 other point mutations have been described in over 50 different positions.¹ Most mutations are pathogenic, although non-amyloidogenic mutations have been reported. TTR is normally involved in the transport of thyroxine and retinol-binding protein. The mutations associated with FAP are thought to cause subtle structural changes that reduce the stability of the TTR tetramer, thereby promoting off-pathway folding and self-assembly in the abnormal amyloid conformation.

Familial TTR amyloidosis most commonly manifests as a polyneuropathy predominantly affecting the sensory and autonomic nervous systems, along with involvement of certain visceral organs. Oculoleptomeningeal amyloidosis due to TTR amyloid deposits in the leptomeninges, brain parenchyma and retina occurs rarely in FAP. It has previously been associated with the TTR Val30 Gly variant² presenting clinically with slowly progressive dementia, seizures, ataxia, hemiparesis and decreased vision without neuropathy. TTR Leu12Pro has been associated with severe peripheral neuropathy, leptomeningeal involvement and substantial visceral amyloidosis.³ We report a patient with a new mutation at TTR Gly53Ala, which to our knowledge has not been reported previously.

CASE REPORT

A 44-year-old woman presented with a 4-year history of personality change, intermittent drowsiness and urinary incontinence. She had become introverted and depressed, with slurred speech and balance difficulties.

There was a history of increasingly severe, episodic headaches since 18 years of age, which had been labelled as migraines. For the past 3 years these had occurred every few days with either an aura of facial weakness and slurred speech or right-sided sensory disturbance in the limbs, which could progress to a hemiparesis. She would then develop a throbbing headache with associated nausea and photophobia. On one occasion she developed a migraine aura and was found by her sister 2 days later with no memory of the previous 48 h. She was admitted to

hospital for investigation of a possible subarachnoid haemorrhage.

Neurological examination showed her to be initially aphasic with right hemiparesis and prosopagnosia, and with a slow and slurred speech.

Cranial nerve examination including funduscopy was normal. She had reduced sensation to light touch and pin prick in both hands, incoordination of all limbs and gait, brisk reflexes and bilateral extensor plantar responses. She scored 29/30 in the Mini-Mental State Examination.

Computed tomography scan of the brain was normal. Lumbar puncture showed high cerebrospinal fluid (CSF) protein at 7.23 g/l, but was otherwise normal. Magnetic resonance imaging of the brain with contrast showed diffuse leptomeningeal thickening with enhancement mainly in the pia mater, particularly over the temporal lobe. Electrocardiography and abdominal ultrasonography were normal. Echocardiography showed concentric thickening of the left ventricular wall. Nerve conduction studies showed mildly reduced sural nerve action potentials (7 mv). The patient had proteinuria (4.8 g/24 h). Rectal, bladder wall and sural nerve biopsies were negative for amyloid. Serum amyloid P component scintigraphy did not show any visceral amyloid deposits. Endomyocardial biopsy showed substantial amyloid deposits that stained specifically with antibodies to transthyretin (fig 1). This staining could be completely blocked by absorption of the antibodies with pure TTR.

Gene sequencing with amplification and direct sequencing of all four exons of the TTR gene showed the patient to be heterozygotic for a single base change in one allele of exon 3, altering the codon for residue 53 of the native protein from glycine (GGA) to alanine (GCA)—that is, Gly53Ala. The remainder of the sequence was normal.

Neuropsychological testing showed a verbal IQ of 87 and a performance IQ of 79, with a decline in memory performance and inefficiency in tests of frontal lobe functioning.

The neuropsychological testing when repeated 2 years later showed deterioration with a verbal IQ of 70, performance IQ of 65 and extremely slow rates of information processing.

The patient had impaired attention and working memory skills, with reduced verbal fluency and verbal comprehension skills.

She currently requires 24 h help from carers for all activities of daily living. Now there is also clinical and neurophysiological evidence that she has a severe axonal neuropathy.

The possibility of orthotopic liver transplantation was considered after the diagnosis, but owing to her poor general and cognitive state and the uncertainty of its effect in this case, as there was central nervous system (CNS) involvement, it was not pursued further.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; FAP, familial amyloid polyneuropathy; TTR, transthyretin

Figure 1 Cardiac ventricular tissue stained with Sirius Red, showing characteristic dichroic birefringence pattern of amyloid.

Detailed family history showed that her father presented at the age of 62 years with progressive ataxia associated with peripheral neuropathy, cognitive impairment and posterior vitreous opacities. He also had renal impairment, left ventricular hypertrophy and complete heart block. Investigations showed cortical atrophy and sensori-motor axonal neuropathy. A biopsy of a penile ulcer confirmed amyloidosis, but the aetiology was not investigated further. He died from a combination of cardiac and renal failure. Both he and his other daughter had migraines. No other family members were known to have neurological illnesses.

DISCUSSION

The clinical features and laboratory investigations in this case extend the phenotype and genotype associated with familial amyloid polyneuropathy. Our patient presented with migraine-like headaches before she developed progressive ataxia and cognitive decline. Neuropathy was a late feature, and sub-clinical cardiac amyloid was present.

In hereditary amyloidosis associated with TTR mutations, peripheral and autonomic neuropathy with or without cardiac amyloidosis are the most common manifestations. Varying degrees of vitreous and visceral involvement are not uncommon but tend to be subclinical. CNS involvement is rare. Petersen *et al*² described a kindred affected by a slowly progressive dementia, seizures, ataxia, hemiparesis and decreased vision without neuropathy, in which TTR amyloid deposits were present in the leptomeninges, brain parenchyma and eye. This syndrome, which has been described in the literature as oculoleptomeningeal amyloidosis, was associated with the substitution of valine with glycine at TTR residue 30. Isolated manifestations in the CNS such as dementia, depression, seizures, cerebral infarction or haemorrhage, due to leptomeningeal amyloidosis, have been reported in families carrying other TTR variants including Tyr69His,⁴ Asp18Gly, Val30Gly and Tyr114Cys.³ The most common mutation, TTR Met30, can also cause CNS amyloidosis along with its other presentations.⁵ Gadolinium-enhanced magnetic resonance imaging of the CNS may detect leptomeningeal amyloid deposition, as it did in our patient, even at a presymptomatic stage of CNS involvement.⁶ Ellie *et al*¹³ reported cases of meningocerebrovascular amyloidosis in a kindred with a gene mutation at the same position as in our patient (residue 53; Gly53Glu), raising the possibility that disruption of this particular part of the TTR molecule might result in preferentially CNS amyloid deposition.

Plasma TTR acts as a transport protein for thyroxine in the serum and cerebrospinal fluid, and might contribute to the transport of serum thyroxine across the blood-brain and blood-choroid-plexus-CSF barriers.⁸ Although >98% of circulating TTR is derived from the liver, expression of TTR mRNA in the human choroid plexus can be 40 times greater than in the liver,⁹ potentially contributing to direct CNS amyloid involvement.

Liver transplantation was introduced as a treatment for FAP 15 years ago, and the procedure results in >95% reduction in the circulating concentration of variant TTR.¹⁰ Liver transplantation has been most beneficial in patients with early peripheral neuropathy associated with the Val30Met variant, showing slower rate of loss of myelinated axons in biopsied nerves, and possibly stabilisation of motor and sensory dysfunction along with a subjective improvement in symptoms.¹¹ Patients with non-Val30Met variants and those with cardiac involvement have fared less favourably after liver transplantation.¹⁰ Liver transplantation would not prevent ongoing deposition of amyloid in the subarachnoid space and leptomeninges arising from variant TTR production in the choroid plexus.¹² Vitreous amyloidosis occurred in a patient with FAP due to Val30Met after their liver transplant, owing to ongoing intraocular synthesis of mutant TTR.¹³ The CSF concentrations of variant TTR investigated in four patients with FAP after liver transplantation were shown to be constant in two and to fall by about 50% in the other two.¹³ Progressive amyloidosis after liver transplantation can also occur as a result of wild-type TTR continuing to be deposited on the template of amyloid already present at the time of surgery. This phenomenon has been best characterised in the heart.¹⁰

This TTR mutation seems to be associated with worsening migraine headaches at presentation, followed by focal cerebral pathology. The most likely mechanism for this is cerebral ischaemia due to leptomeningeal vessel amyloidosis.³ The other two postulated mechanisms for cerebral dysfunction in TTR CNS amyloidosis are hydrocephalus secondary to amyloid infiltration of the meninges, and superficial siderosis due to recurrent haemorrhages, neither of which was present in this patient. Recognising this presentation of TTR with increasingly severe migraine-like headaches often with a focal neurological deficit and markedly raised CSF protein could allow for earlier diagnosis of such patients.

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Informed consent was obtained from the patient for publication of her details in this paper.

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HISTORICAL NOTE

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Johann Bernhard Aloys von Gudden: an outstanding scientist

Johann Bernhard Aloys von Gudden was a visionary psychiatrist and neuroanatomist. He dedicated himself to neurobiology and was far more than a consulting psychiatrist to the Bavarian royal family. Some well-known scientists such as Emil Kraepelin (1856–1926), Franz Nissl (1860–1919), Auguste-Henri Forel (1848–1931) and Sigbert Josef Maria Ganser (1853–1931) studied under his supervision.

von Gudden was born in Kleve, in lower Rhineland near the Dutch frontier, on 7 June 1824. He was the third of seven sons of Johannes Gudden, a landed proprietor, owner of a brewery and member of the town council. In 1843, he began his studies in philosophy and medicine at the university in Bonn. For his doctoral dissertation, von Gudden studied torsional eye movement under the supervision of Alfred Volkman (1800–77) at Halle. He received his medical degree in 1848 and in the same year passed with distinction the state medical examination in Berlin. Thereafter, he obtained a position at the Siegburg asylum as an assistant under the supervision of Karl Wigand Maximilian Jacobi (1775–1858), one of the leading German psychiatrists.

After completing his studies in Berlin in 1849, von Gudden served in the army for a year. From 1851 to 1855, he worked with Christian Friedrich Wilhelm Roller (1802–78) in the Illenau asylum near Achern, the first modern psychiatric hospital in Germany. He married Roller's granddaughter Clarissa Voigt in 1855, and, in the summer of the same year at the age of 31, was appointed the director of Werneck, a newly established asylum in northern Bavaria. In October 1869, von Gudden became director of the newly founded Burghölzli psychiatric hospital in Zürich, Switzerland, and in 1870, was appointed co-editor of *Archiv für Psychiatrie und Nervenkrankheiten*. In 1872, he took over the direction of the Oberbayerische Kreis-Irrenanstalt in Munich, and subsequently became a full professor of psychiatry at the University of Munich.

At the height of his career, von Gudden was commissioned to provide psychiatric care for the Bavarian royal family. He was the personal doctor of the mentally diseased Crown Prince Rudolf Otto (1848–1916) for many years. He took responsibility for the everyday care of the crown prince, who was secluded in Furstentried, a castle near Munich, and subsequently was assigned to examine and treat King Ludwig II of Bavaria (1845–86). On 13 July, 2 days after King Ludwig II was arrested at Castle Neuschwanstein, Ludwig II and Bernhard von Gudden drowned in Starnberg Lake, close to the castle of Berg. The details surrounding their death remain unclear. For some incomprehensible reason, no autopsy was ever performed on von Gudden to determine the cause of death.

In the last 14 years of his life, von Gudden devoted himself to the study of neuroanatomy, a rapidly developing science in the 19th century. He was the first neuroanatomist to create lesions in the nervous system of newborn animals and to study the subsequent anatomical changes. In this work, he applied the

technique of secondary degeneration to study important inter-relationships between the cortical and subcortical structures. Today, this method, based on retrograde neuronal cell body changes observed after nervous system lesions, is still referred to as the von Gudden method. A published article¹ shows that he was clearly aware of the limitations of this method; he was not so much interested in the description of brain centres, but was concerned with the independencies and connections between the centres.

Macroscopic observation was widely used in von Gudden's time, as microscopy was still unsatisfactory. Therefore, he pioneered the development of a microtome, the so-called Gudden's microtome,² for sectioning the human brain, and using this he described the important neuroanatomical centres. His assistant, Auguste-Henri Forel, subsequently improved the microtome, and thus he was able to obtain entire human brain sections, at about 55 µm in thickness.

von Gudden is perhaps best known for his studies on partial decussation of the optic paths, a subject that kept him occupied for around 30 years. His method of producing secondary atrophy of central structures after the removal of sense organs or cranial nerves in young animals ushered in a fresh advance in experimental neurology. In fully grown animals, from which eyes had been removed when they were young, he showed not only crossed and uncrossed optic fibres but also a supraoptic commissure and the transverse peduncular tract. Both of these tracts now bear his name. He was the first to describe the interpeduncular nucleus and the tegmental nuclei, known to all who work in the midbrain today as the dorsal and ventral nuclei, respectively, of Gudden.

One of Gudden's greatest contributions was his observation in 1870 that destruction of certain areas of the cerebral cortex leads to atrophy of specific thalamic nuclei. Augustus Volney Waller believed that, after a cut, the cell body and central stump of the nerve remained normal, but Gudden found that they showed signs of atrophy. Accordingly, he launched a series of investigations in which he used his "secondary degeneration technique"—that is, the Gudden method—to trace connections between the main centres of the brain.

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