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P. P. Urban
C. Hertkorn
J. M. Schattenberg
J. Gawehn
S. Hägele
M. Wunsch
K. Altland

Leptomeningeal familial amyloidosis:

A rare differential diagnosis of leptomeningeal enhancement in MRI

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Sirs: We report on a 31-year old woman with a known history of familial amyloidosis with the transthyretin (TTR) variant Leu12Pro. The pedigree can be traced back to the year 1780. For three years the patient had suffered from a primary partial secondary generalising epilepsy with a constant semiology starting with spitting automatisms, indicating a focus of the non dominant hemisphere [15]. Interestingly, the mother of our patient also suffered from epilepsy with the same semiology and developed severe bilateral visual impairment in her later life. The patient was admitted to our hospital because she became increasingly drowsy and had developed a delusional state at the same time as pneumonia. The patient had received a liver transplant nine months previously and was on a stable immunosuppressive medication (Cyclosporine 100 mg/d, mycophenolate mofetil 1000 mg/d). Clinically, the patient was drowsy and not well orientated regarding time, place and person. All other findings were completely normal and there were no clinical and electrophysiological signs of peripheral neuropathy. Two days later under antibiotic treatment for pneumonia with cefuroxim the patient showed normal vigilance, was fully orientated but showed slight attention deficits leading to a mini mental score (MMSE) of 27 points. The electroencephalogram showed a diffuse (6 Hz) and focal bitemporal slowing without epileptiform discharges. Cerebrospinal fluid examination revealed a normal opening pressure but xanthochromia with an increased protein level of 229 mg/dl and normal cell count (2/mm^3), cell cytology, glucose CSF/serum-ratio, and lactate. Tests for oligoclonal bands in the CSF were negative. Magnetic resonance imaging (MRI) showed in the T1 images after contrast administration a diffuse leptomeningeal enhancement around the brainstem, cerebellum and lower parts of the cerebral sulci. No focal intracerebral abnormalities were detected in T2* images.

The ophthalmologic examination was completely normal including split lamp investigation and electroretinogram.

The MRI and CSF findings together with the known familial amyloidosis indicate a leptomeningeal involvement due to TTR accumulation [12]. This is the second report of a leptomeningeal amyloidosis with a Leu12Pro TTR gene mutation, which was initially described by Brett et al. [5]. Several different TTR gene mutations have been shown to cause this form of amyloidosis (Asp18Gly, Val30Met, Val30Gly, Phe64Ser, Ala36Pro, Gly53Glu, Tyr69His, Ala25Thr, Tyr114Cys) (see [9]). Some of the TTR gene mutations have been associated with both central and peripheral nervous system disorders, whereas others have been characterized mainly by CNS symptoms, including dementia, seizures, ataxia, and stroke-like episodes. By contrast to non–familial forms of amyloidosis, susceptibility irregularities within the cerebral parenchyma were not observed in our patient.

The mainstay of therapy in familial amyloidosis is liver transplantation. However, recently it was shown that oculeptomeningeal involvement is not prevented in all patients with initial familial amyloidotic polyneuropathy [2]. In this study, out of 22 patients, three patients developed ocular involvement and two patients exhibited de novo amyloid deposition in the leptomeninges after transplantation, all patients with a Tyr114Cys TTR gene mutation. This observation might be explained by TTR synthesis by the retina and choroid plexus demonstrating the need for additional treatment options like gene therapy [11] or drug interference with the pathogenetic

P. P. Urban (✉) · S. Hägele
Department of Neurology
University of Mainz
Langenbeckstr. 1
55101 Mainz, Germany
Fax: +49-6131/175-625
E-Mail: urban@neurologie.klinik.uni-mainz

C. Hertkorn · J. M. Schattenberg
Department of Internal Medicine
University of Mainz
Germany

J. Gawehn
Institute of Neuroradiology
University of Mainz
Germany

M. Wunsch
Department of Transplantation and Hepatobiliary Surgery
University of Mainz
Germany

K. Altland
Insitute of Human Genetics
University of Giessen
Germany

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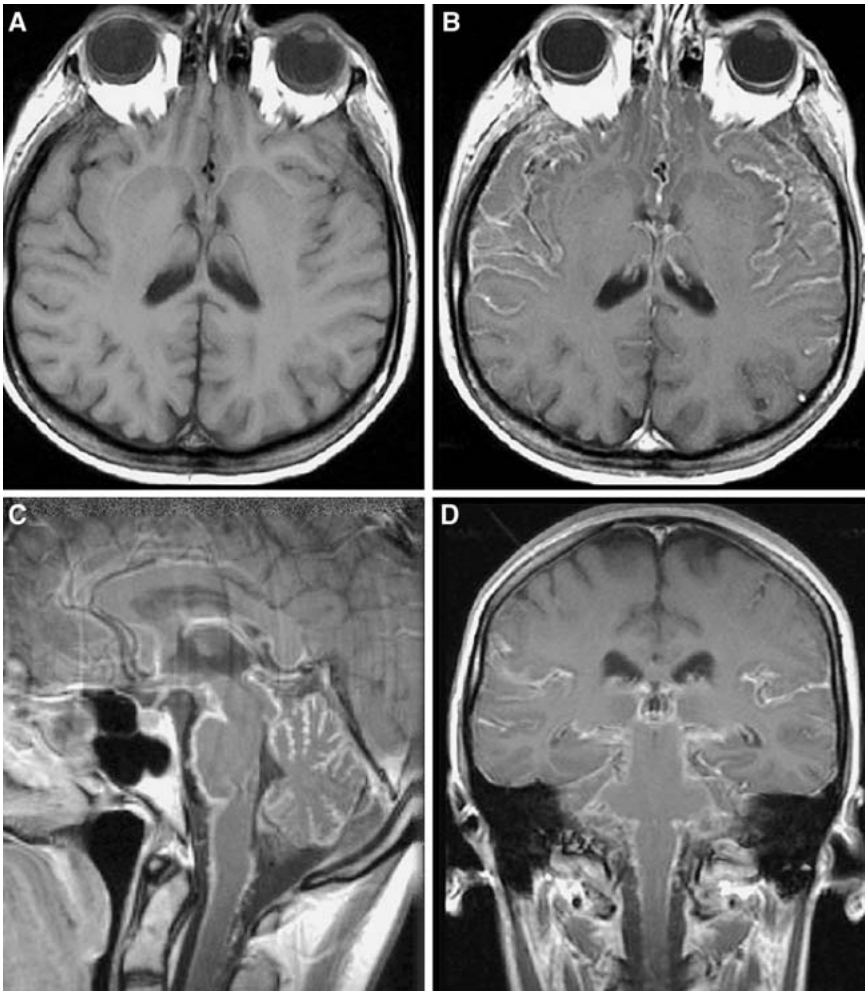

Fig. 1 T1-weighted image in temperal orientation (**A**). Same slice contrast enchanced (**B**). Sagittal aspect after contrast application (**C**). Coronal view of striking meningeal thickening (**D**).

protein folding process, such as sulfite [1], flufenamine acid [14], and 4′-iodo-4′-deoxydoxorubicin [13] but there have been no controlled studies concerning the risk and efficacy of the aforementioned drugs. In our patient, we do not know for how long the leptomeningeal involvement has been present, since a contrast enhanced brain MRI was not performed before liver transplantation.

However, the MRI pattern of leptomeningeal enhancement is not specific for amyloidosis and is also seen in other conditions, like infectious meningitis of different origin [4], systemic autoimmune or vasculitic disorders like neurosarcoidosis [8] or Wegener's granulomatosis [7], meningeal carcinomatosis [6], chronic intracranial hypotension [5]. Infrequently, meningeal thickening may be related to other fibrosclerotic diseases such as sclerosing cholangitis [3]. However, in a small number of patients the etiology of leptomeningeal enhancement remains unclear, which must be proved by biopsy and is than called idiopathic hypertrophic pachymeningitis [10].

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