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# Surgically treated intradural spinal manifestation of hereditary amyloidogenic transthyretin amyloidosis - A case report and scoping review of the literature

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ABSTRACT

*Introduction:* Hereditary transthyretin amyloidosis (ATTRv) is an autosomal-dominant disorder, where a TTR mutations lead to amyloid fibril deposits in tissues and consecutively alter organ function. ATTRv is a multisystemic disorder with a heterogeneous clinical presentation. Spinal leptomeningeal depositions are described only scarcely in the literature.

*Research question:* We present a rare case of surgically treated intradural, extra-medullary amyloidosis with respective clinical, diagnostic and surgical features to raise awareness of this rare entity.

*Material and methods:* Clinical, radiological and operative characteristics were retrieved from the electronical patient management system. Additionally, a scoping literature review on leptomeningeal spinal manifestations of ATTRv was performed.

*Results:* A 45-year-old man with a known ATTRv presented with gait disturbance and paresis of the lower extremities. He had been treated with the siRNA therapeutical Patisiran for 13 months under which his symptoms worsened. An MRI of the spine revealed spinal cord compression with myelopathy at the level of T2 with anterior dislocation of the spinal cord due to an intradural, extramedullary lesion. A laminectomy and opening of the dura with a complete resection of the lesion was performed. The histological examination of the biopsy showed amyloid deposits. At six-month follow-up the patient showed complete normalization of the paresis, gait, sensory and urinary disturbances and resumed his work.

*Discussion and conclusion:* Spinal leptomeningeal deposition of amyloid is a rare occurrence within the framework of ATTRv. Micro-neurosurgical complete resection of the lesion is feasible in patients with preoperative myelopathic symptoms and resulted in complete symptom relief in this case.

## 1. Introduction

Hereditary transthyretin amyloidosis (ATTRv) is a progressive, devastating and often fatal disease which is generally under recognized and can lead to a substantial disease burden (Gertz et al., 2020; Stewart et al., 2018). It is characterized as an autosomal-dominant disorder due to mutation of the transthyretin (*TTR*) gene located on the chromosome 18q12.1 leading to the pathologic protein aggregation in different organs (Manganelli et al., 2020). Until now, over 130 pathologic variants involving the *TTR* gene have been described (Manganelli et al., 2020). Only few of these have been identified to involve the leptomeninges. Amyloid deposits involving the leptomeninges of the spinal cord may have a compressive effect causing neurological deficits, and should therefore be considered, especially in patients with a positive family history or a diagnosis of ATTRv

*Abbreviations:* ATTRv, hereditary transthyretin amyloidosis; EMA, epithelial membrane antigen; MRI, magnetic resonance imaging; siRNA, small interfering RNA; TTR, transthyretin.

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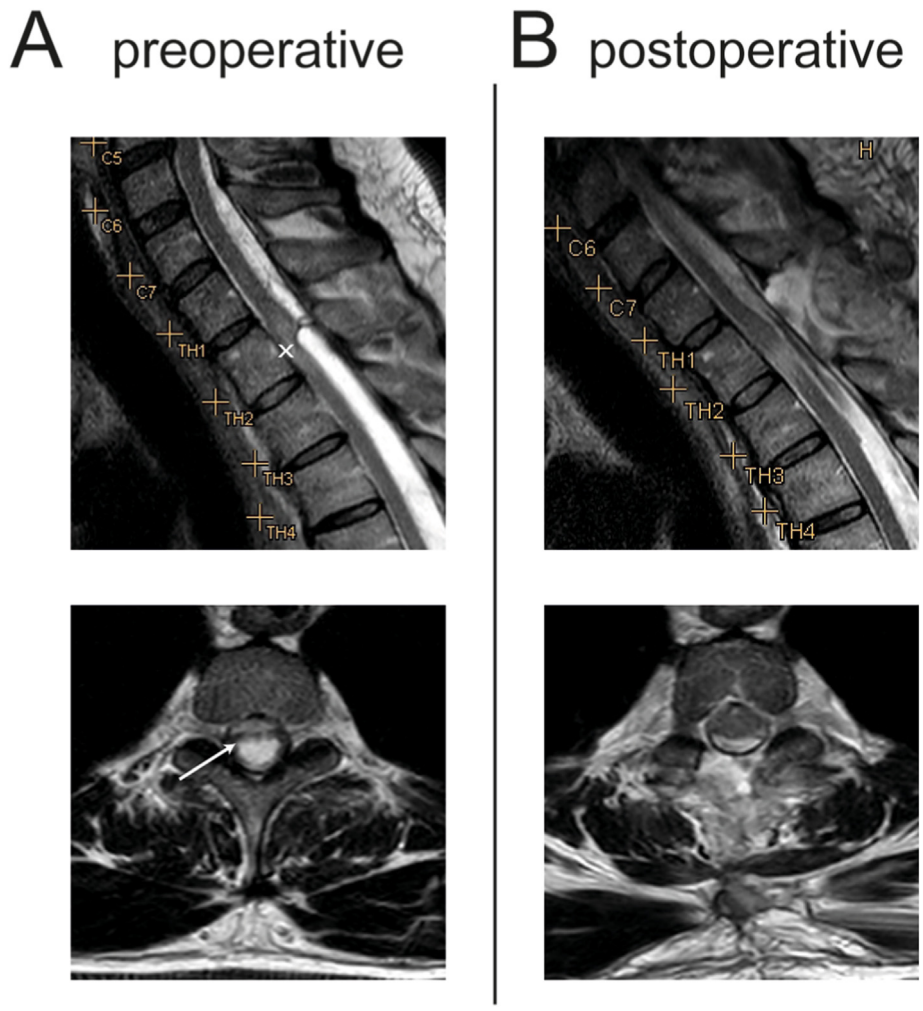


**Fig. 1.** Pre- and postoperative spine MRI. Pre- (A) and postoperative (B) T2-weighted sagittal (upper) and axial (lower row) MRI series. Asterix (sagittal) and arrowhead (axial section) shows the site of the spinal cord compression.

(Dalolio et al., 2017). To the best of our knowledge, only one case of ATTRv with leptomeningeal deposition has been described previously. This TTR subtype was associated with a mutation at c.381T>G (p.Ile127Met)(Mathieu et al., 2018).

We here present a rare case of amyloid-induced spinal cord compression in a patient with ATTRv and present a systematic literature review of spinal intradural involvement in hereditary amyloidosis.

## 2. Methods

### 2.1. Ethical considerations and consent for publication

All information were extracted from our institutional patient registry and by retrospective chart review. The institutional registry has been approved by the local ethical review board ("Kantonale Ethikkommission Zürich", identifier PB-2017-00093). Additionally, individual informed patient consent was obtained including consent for publication, and this study was performed in accordance with the ethical standards of the institutional, local ethics regulations and with the 1964 Helsinki declaration and its later amendments.

Manuscript preparation was done according to the CARE checklist for clinical case reports (Gagnier et al., 2013).

### 2.2. Systematic literature review

A literature review was performed according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) protocol (Tricco et al., 2018). A specific review protocol does not exist as we elaborate the methodology in the following: Literature published between 1900 and 2021 was searched (August 01, 2021) on PubMed, Science Direct and Google Scholar databases with the following search term: "systemic" AND "amyloidosis" AND "deposition" AND "hereditary" AND "transthyretin" AND ("spine" OR "spinal") AND ("leptomeningeal" OR "intradural" OR "extramedullary"). The identified articles were assessed with the inclusion and exclusion criteria. Inclusion criteria included published case reports or studies written in English language and evaluating patients with a confirmed hereditary transthyretin amyloidosis and leptomeningeal amyloid deposition involving the spine. Exclusion criteria comprised patients with only localized disease (as for example in solitary spinal amyloidomas), amyloid deposition in a different location (e.g. ligamentum flavum) or in case of amyloidosis with another amyloidogenic protein (e.g. light-chain amyloidosis). Searching in citations of derived articles was used to identify additional articles for the screening process. The same in- and exclusion criteria applied for these additional articles. See Fig. 4 for the scoping review inclusion flow-chart. The following data items were extracted from the included articles, if available: patient demographics (age, sex), presenting symptoms, diagnosis with anatomical distribution, identified mutation and operative treatment characteristics as well as postoperative course. All retrieved data was accumulated in Table 2 to get an overview and to compare the existing cases from the literature.

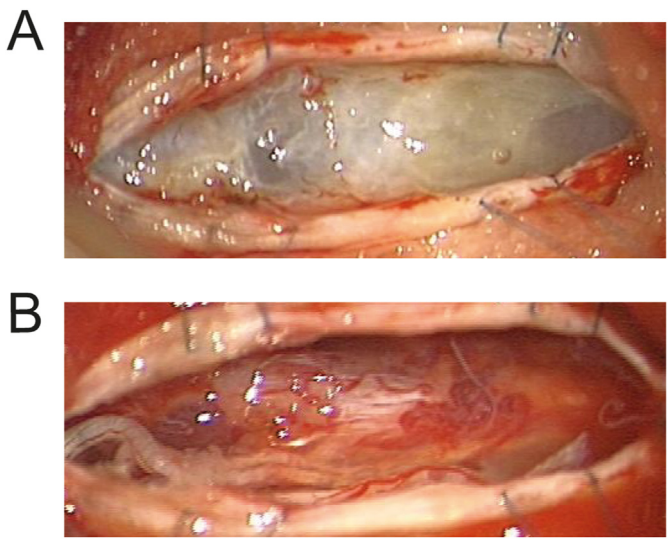


**Fig. 2.** Intraoperative view. Intraoperative, intradural view before (A) and after (B) resection of the amyloid deposits. After dural opening: (A) shows the glossy white colored amyloid deposit. (B) spinal cord with peri-medullary vessels come into view after complete resection of the lesion.

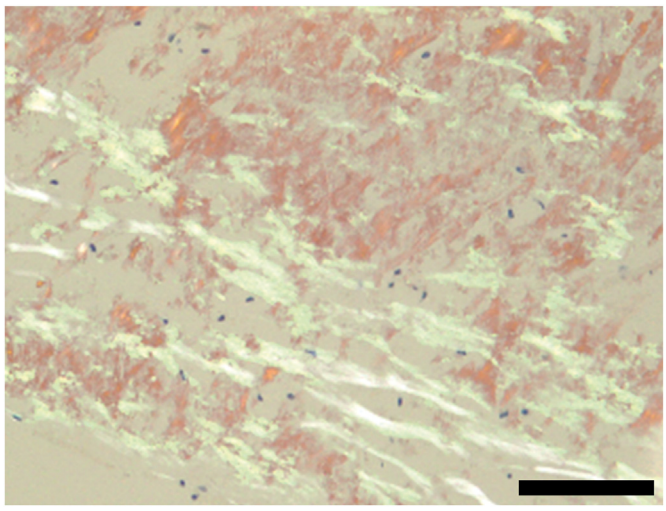

**Fig. 3.** Histopathological specimen Histological specimen: The biopsy showed scattered connective tissue and predominantly amorphous material. The latter corresponded to amyloid under polarizing light (green) with Kongo Red staining. Scale bar corresponds to 100μm. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Article assessment for in- and exclusion criteria was done by two of the authors independently.

## 3. Results

### 3.1. Clinical presentation

A 45-year-old man was admitted to our neurosurgical outpatient clinic with progressive gait disturbance and voiding dysfunction. He additionally complained of radiating pain in both legs especially at standing up and associated with dysesthesias of both shins. Altogether, this resulted in an impaired mobility and walking stick dependency with a maximum walking distance of about 50 m. These symptoms had progressed slowly over four years and worsened more rapidly in the past few months. The patient had been treated with the siRNA Patisiran from September 2019 onwards without alteration/improvement of his condition.

### 3.2. History

The patient's anamnesis revealed a ATTRv with positive family history, diagnosed two years earlier. His mother, who had passed away eleven years after a liver transplantation, had suffered from ATTRv with neurological and cardiac involvement. The underlying mutation - c381T>G (p.(Ile127Met) - is also carried by his sister and suspected in his maternal grandfather, uncle and cousin. In the past, he had undergone surgeries for bilateral carpal tunnel syndrome. The patient's cardiac involvement is mild (stage 1 in the staging system Gillmore et al. (2018)) with no limitation in his everyday life.

### 3.3. Examination/diagnostics

Upon neurological examination, the patient presented with an unstable and markedly prone gait. Romberg's test was positive. Paresis of the lower extremities was present in hip flexion and extension of the left leg (M3; using the Medical Research Council grading system) but was also slightly decreased in the right leg (M4). Hypesthesia was present in both legs from the knees downwards. He had a bilateral positive Babinski sign. Achilles tendon reflex was symmetrically decreased in both legs.

A magnetic resonance imaging (MRI) of the spinal cord showed an anterior displacement of the spinal cord with posterior intradural septation and focal spinal cord compression at the level of Th2 (see Fig. 1A). At this level, the dorsal caudal arachnoid space was widened showing a so-called “scalpel sign”, suggesting the presence of a spinal arachnoid web (see Fig. 1A)(Voglis et al., 2021). A brain MRI was performed during disease course to screen for intracranial amyloid deposits and showed normal findings.

### 3.4. Surgery

Due to the congruence of the clinical and radiological findings, a microsurgical laminectomy at the level of Th2 and resection of the intradural lesion was discussed with the patient.

A Th2 laminectomy (bony removal of the lamina at level Th2) was performed and the transdural ultrasound confirmed the correct localization as well as the compressed and ventrally dislocated spinal cord. Next, the dural sac was opened to expose the lesion (see Fig. 2 and Additional file 1). The focal, avital tissue layer adjacent to the spinal cord appeared in a glossy white-beige color, rather atypical for an arachnoid web. Before proceeding with the circumferential detachment of the spinal cord and dura, tissue samples were taken for histopathological workup. After complete resection of the lesion, water-tight dura closure and usual wound closure was performed. Postoperatively he did not have any new focal neurological deficits.

### 3.5. Histopathology

The histopathological examination described multiple large-scale congophilic amyloid deposits within the amorphous material (see Fig. 3). Green birefringence under polarized light as well as an immune reaction with the antibody against ATTR could be observed. The incised leptomeningeal tissue was marked with epithelial membrane antigen (EMA) and showed no reaction against ATTR. Thus, leptomeningeal amyloid deposits could be confirmed as a diagnosis.

### 3.6. Postoperative course

Postoperative imaging revealed complete resection of the lesion with a decompressed spinal cord and a now better delineable slight myelopathy signal (see Fig. 1B). The patient did not develop any new neurological deficits or symptoms, but rather the initial symptoms resolved

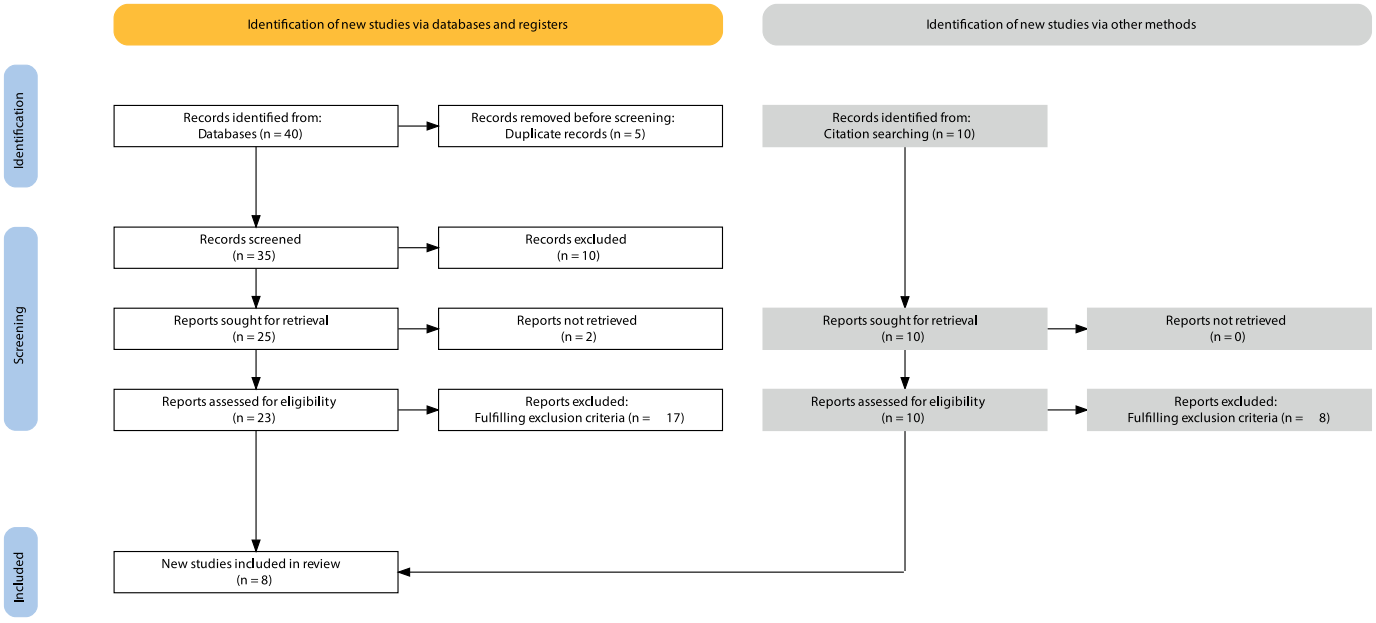


**Fig. 4.** Flow-chart literature review.

mostly until discharge one week after admission.

Patisiran therapy was resumed right after surgery. Follow-up consultations took place eight weeks and six months postoperatively. The gait disturbances, sensory and urinary dysfunction as well as the paresis were completely resolved, and the patient had resumed his work at the six months follow-up visit. An MRI six months after surgery showed no residual or recurrence of the intradural amyloid deposits.

### 3.7. Literature review

A total of eight articles met the inclusion criteria (see methods section) and were included in our literature overview. The total cohort consisting of eight individual patients with ATTRv and leptomeningeal amyloid deposition were analyzed regarding demographics, clinical features, diagnosis, mutation, surgical intervention and postoperative

**Table 1**
Previously described mutations associated with leptomeningeal phenotype in general.

| | Mutation | Ethnicity | Phenotype | Comment | References |
|---|---|---|---|---|---|
| 1 | Leu12Pro (p.Leu32Pro) | British | LM, PN, AN, H, L | Included in Table 2 | Brett et al. (1999), Brain 122, 183 10.1093/brain/122.2.183 |
| 2 | Asp18Gly (p.Asp38Gly) | Hungarian | LM | 56 subjects, no description of location of amyloid deposits and treatment | Vidal (1996) Am J Pathol 148, 361 https://pubmed.ncbi.nlm.nih.gov/8579098/ |
| 3 | Val30Met (p.Val50Met) | American, Chinese, Japanese, European | LM, AN, E, PN | focuses on molecular processes | Saraiva (1984) J Clin Invest 74, 104 10.1172/JCI111390 |
| 4 | Val30Gly (p.Val50Gly) | American | LM, CNS, E | Not retrieved | Peterson (1997) Ann Neurol 41, 307 10.1002/ana.410410305 |
| 5 | Thr49Pro (p.Thr69Pro) | American | LM, H | Included in Table 2 | Nakagawa et al. (2008) J Neurol, 272 (1–2):186 10.1016/j.jns.2008.05.014 (Connors (2003) Amyloid 10, 160) |
| 6 | Gly53Arg (p.Gly73Arg) | American | LM | Brain CT showed diffuse leptomeningeal involvement, no mention of spinal involvement | Liepnieks (2011) Amyloid 18; 1:162 10.3109/13506129.2011.574354060 |
| 7 | Gly53Glu (p.Gly73Glu) | French | LM, CNS, N | no involvement of spine described | Ellie (2001), Neurology 57, 135 10.1212/wnl.57.1.135 |
| 8 | Gly53Ala (p.Gly73Ala) | British | LM, AN, E, H, PN | no involvement of spine described | Douglass (2007) J Neurol Neurosurg Psychiatry 78, 193 10.1136/jnnp.2006.093500 |
| 9 | Leu55Arg (p.Leu75Arg) | Chinese, German | LM, PN, E | focuses on vitreous amyloidosis | Long (2012) Opthalmic Genet 33(1):28-33 10.3109/13816810.2011.599356 (Connors (2003) Amyloid 10, 160) |
| 10 | Phe64Ser (p.Phe84Ser) | Canadian (Italian), British | LM, E, PN, CNS | amyloid in ligamentum flavum led to compression of spinal cord | Uemichi (1999) Arch Neurol 56, 1152 10.1001/archneur.September 56, 1152 |
| 11 | Ile84Ser (p.Ile104Ser) | Hungarian, Swiss, American | LM, CTS, E, H | postmortem study | Dwulet (1986) J Clin Invest 78, 880 10.1172/JCI112675 |
| 12 | Tyr114Cys (p.Tyr134Cys) | Japanese | LM, AN, E, H, PN | no involvement of spine described | Ueno (1990) Biochem Biophys Res Commun 169, 143 10.1016/0006–291x(90)91445-x |

Overview of known TTR mutations causing a leptomeningeal phenotype with the respective references and spinal involvement status. Adapted from http://amyloidosismutations.com/mut-attr.php.
AN = autonomic neuropathy; CTS = carpal tunnel syndrome; E = eye; H = heart; K = kidney; L = liver; LM = leptomeningeal; N = neuropathy; PN = polyneuropathy; CNS = central nervous system.

**Table 2**
Reported cases in the literature with spinal amyloid deposits in hereditary amyloidosis.

| | Case | Sex/Age | Symptoms | Diagnosis, level | Mutation | Resection, treatment | Postoperative development |
|---|---|---|---|---|---|---|---|
| 1 | Mathieu F. et al., 2018 (Mathieu et al., 2018) | M (53y) | Progressive weakness in upper and lower limbs, ataxia, peripheral and autonomic neuropathy | Oculoleptomeningeal amyloidosis with diffuse leptomeningeal enhancement along the brainstem and spinal cord (plus evidence of hemosiderosis) | p.Ile127Met mutation | T12-L1 laminectomy for biopsy of lesion Ongoing medical management with tafamidis. | n.s. |
| 2 | Nakagawa K. et al., 2008 (Nakagawa et al., 2008) | M (53y) | Recurrent episodes of transient aphasia, stiffness of the right hand, headaches and peripheral neuropathy | Diffuse leptomeningeal amyloidosis from entire cortical sulci to cauda equina | Thr49Pro mutation | Biopsy of superficial cortex and leptomeninges | n.s. |
| 3 | Shimizu, Y. et al., 2009 (Shimizu et al., 2006) | M (48y) | Intermittent vertigo, dysesthesia in both legs and left hand, inability to walk | Leptomeningeal amyloidosis with linear enhancement from brain surface to cauda equina and demyelinating polyneuropathy | Ala25Thr mutation | Open biopsy at Th11-12 | After 2 years no significant progression of disease and no new areas of weakness or sensory loss |
| 4 | Liu KC J., 2015 (Liu et al., 2015) | F (60y) | Progressively worsening gait imbalance, lower extremity weakness and decreased mental alertness | Oculoleptomeningeal amyloidosis with intrathecal lesion from midcervical to lumbar spine | n.s. | Laminectomy L3-L5, open biopsy of lesion (no attempt of further decompression due to extent of ossification) | n.s. |
| 5 | Jin K. et al., 2004 (Jin et al., 2004) | M (42y) (Patient 1) | Unsteady and ataxic gait, dysuria and erectile disorder | Familial leptomeningeal amyloidosis with diffuse leptomeningeal enhancement along sylvian fissures, brainstem, cerebellum and spinal cord | Asp18Gly mutation | Th1 hemilaminectomy and leptomeningeal biopsy | After eight months unsteady gait during several episodes of dull headache, no worsening of neurological findings |
| 6 | McColgan P. et al., 2015 (McColgan et al., 2015) | M (43y) | Rapidly progressive neurological decline with erectile difficulties, urinary urgency and incontinence, paresthesias in both feet | Oculoleptomeningeal amyloidosis with extensive leptomeningeal enhancement over surface of brain and spinal cord | Leu12Pro mutation | Brain biopsy | Gradual decline in overall condition and development of atonic bladder |
| 7 | Brett M. et al., 1999 (Brett et al., 1999) | F (38y) | Ascending sensorimotor polyneuropathy, severe autonomic dysfunction with urinary retention and constipation, ataxia | Oculoleptomeningeal amyloidosis and familial amyloid polyneuropathy with leptomeningeal amyloidosis with enhancement of cerebral and spinal meninges | Leu12Pro mutation | Posterior fossa meningeal biopsy | No deterioration, patient died 13 months after the surgery |
| 8 | Herrick M.K. et al., 1996 | F (69y) | Progressive bilateral lower extremity weakness, incontinence, confusion | Familial amyloidotic polyneuropathy (FAP1) with increasing diffuse leptomeningeal and spinal root enhancement from cervical to sacral region | Val30Met mutation | Cerebral cortical biopsy, later dural and frontal lobe meningeal and cortical biopsy | n.s. |

M = male; F = female; y = years; n.s. = not specified.

development. However, complete data were not retrievable for all subjects. The results are depicted in Table 2. The total cohort consisted of five male and three female subjects, aged between 38 and 69 years (mean age 50.8 years). The following underlying mutations were present in the patients: p.Ile127Met, Thr49Pro, Ala25Thr, Asp18Gly, Leu12Pro and Val30Met. All patients suffered from diffuse or extensive amyloidosis involving most often the brain together with the spinal cord (except case 4). Symptoms varied from motor weakness, sensory and autonomic disturbances as well as progressively worsening gait. All cases were treated surgically for the means to obtain a biopsy and no lesion was amenable for complete resection. Of the four cases that included a follow-up, one patient showed no disease progression (Shimizu et al., 2006), one developed unsteady gait during several episodes of dull headache (Jin et al., 2004), one showed a gradual decline with development of an atonic bladder (McColgan et al., 2015) and one died 13 months after the initial surgery (Brett et al., 1999).

## 4. Discussion

We here present the case of a 45-year-old man with a spinal intradural, extramedullary amyloid deposition with subsequent spinal cord compression and myelopathy and document his favorable clinical course after complete microsurgical excision. Amyloid depositions with compression of the spinal cord are exceptionally rare and accumulation of amyloid in the leptomeninges of the spinal cord in the context of systemic amyloidosis, especially due to a point mutation of the TTR gene at (p.(Ile127Met), has been described only scarcely in the literature.

Generally, the most common intradural, extramedullary lesions consist of meningiomas, neurofibromas, lipomas and metastases (Smitherman et al., 2015).

Amyloidosis describes the extracellular deposition of misfolded and insoluble fibrillar proteins in a twisted β-pleated sheet configuration and can be classified according to the involvement of specific (localized) or multiple organs (systemic disease)(Scott et al., 1986). The disorder can be acquired, which involves misfolded monoclonal κ or λ light chains, serum amyloid A protein and β2-microglobulin, while hereditary forms include transthyretin, apolipoprotein A1, gelsolin, lysozyme, fibrinogen, amyloid-β and cystatin C. Transthyretin is the most common hereditary subtype with the Val50Met mutation being the most prevalent causative mutation (Kaku and Berk, 2019). Besides ATTRv, wild-type transthyretin amyloidosis (ATTRwt) describes formation of amyloid due to an intrinsic tendency of normal protein with a predilection for cardiac involvement (Muchtar et al., 2021; González-López et al., 2017).

ATTRv results from inherited protein mutations within the *TTR* gene located on the chromosome 18q12.1. Transthyretin, a serum precursor protein of amyloid consisting of 127 amino acids, is responsible for the transportation of thyroxine and retinol in the blood and cerebrospinal fluid (Manganelli et al., 2020). It can be destabilized by missense point mutations resulting in amyloid fibrils, which are resistant against protease digestion (Scott et al., 1986; Nakagawa et al., 2008).

So far, over 140 mutations involving the *TTR* gene have been identified, most of them being pathogenic and 12 of them causing a leptomeningeal phenotype. (see Table 1 and http://amyloidosismutations.com/mut-attr.php).

Previously, the deposition of amyloid in the leptomeningeal vessels due to a mutation of the *TTR* gene has been variously described in the literature (see Table 1); however, the mutation at (p.Ile127Met) has frequently been associated with cardiac manifestations. A single case report described the deposition of amyloid in the leptomeninges following a mutation of the *TTR* gene at (p.Ile127Met)(Mathieu et al., 2018). The patient similarly presented with weakness of the extremities, ataxia, sensorimotor deficits and autonomic neuropathy causing urinary retention. In contrast to our case, the amyloid deposition included the brain as well as the spinal cord diffusely and a biopsy for means of diagnosis was the only neurosurgical intervention. As our patient presented with a lesion that was amenable for complete resection, we could document the intraoperative characteristics as well as the postoperative favorable outcome after laminectomy and total resection with a complete regression of his symptoms. The literature review revealed seven more cases which were due to mutations at other sites and most often involved both brain and spinal cord, in contrast to our case which showed no evidence of intracranial involvement. None of the cases in the literature review was treated with complete resection of the spinal lesion, therefore it remains hard to estimate the true suitability of amyloid deposits for surgical resection. Although follow-up data of those patients was scarcely available, symptoms progressed in most of the patients.

Interestingly, the preoperative MRI indicated a so-called "scalpel sign" at the level of Th2, which led to the consideration of a spinal arachnoid web.

Spinal arachnoid webs are intradural formations of thickened arachnoid tissue which subsequently cause spinal cord compression and correlating symptoms (Voglis et al., 2021), similar to the here presented case. Taking the resembling clinical presentation and radiological evidence of both disorders into consideration, we propose that leptomeningeal amyloid deposition should be considered as a very rare differential diagnosis in patients with suspected spinal arachnoid web, especially in patients with evidence of further organ dysfunction, such as heart failure or bilateral carpal tunnel syndrome.

Another differential diagnosis, which can present similarly regarding clinical and radiological signs, is solitary spinal amyloidoma. The localized deposition of amyloid in one organ without evidence of a systemic disease occurs rarely and gives rise to a tumor-like lesion (Pinheiro et al., 2020). Surgical management, consisting of decompression with optional spinal stabilization, proved an excellent outcome in solitary spinal amyloidoma (Werner et al., 2013).

## 5. Conclusions

Leptomeningeal deposition of amyloid (especially secondary to a point mutation of the TTR gene at c381T>G (p.(Ile127Met)) leading to spinal cord compression is a very rare entity in patients suffering from ATTRv. Complete microsurgical resection of symptomatic spinal amyloid deposits seems to be a valid treatment option and resulted in a complete symptom regression in our here presented case.

## Authors' contributions

SV, YY, FvFC curated patient data and prepared the manuscript draft. YY did the literature review. KJH did the histopathological work. LR, DB, RS, MG critically revised the manuscript. MG supervised the study. All authors approved the final manuscript version.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2022.100876.

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