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ORIGINAL COMMUNICATION

Acute necrotizing encephalopathy (ANE1): rare autosomal-dominant disorder presenting as acute transverse myelitis

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Abstract The term "acute transverse myelitis (ATM)" comprises various non-traumatic disorders that eventually can be associated with a focal myelopathy. Patients characteristically present with an acutely occurring paraparesis/plegia and require a comprehensive and timely diagnostic work up for the initiation of an appropriate treatment. We present a case of a 36-year-old female patient with a rare genetic disorder (ANE1: Acute Necrotizing Encephalopathy due to a RANBP2 mutation) who presented with an acute quadriplegia. Following an acute pulmonal infection, she rapidly (< 24 h) developed a severe quadriplegia (total motor score 38) with some facial sensory symptoms (perioral hypoesthesia). Magnetic resonance imaging (MRI) revealed a combination of longitudinal extensive transverse myelitis and symmetrical thalamic lesions. A work-up for infectious and systemic diseases was negative; specifically, no findings related to multiple sclerosis, neuromyelitis optica or vascular disorders. After empirical high dose steroid treatment and rehabilitation therapy, the patient gained almost normal gait and upper limb function. She was found to carry an autosomal-dominant missense mutation in the RANBP2 gene predisposing for ANE. Gene segregation was confirmed in other family members that had been affected by other episodes of acute steroid-responsive encephalopathies. We propose that a redefined diagnostic workup of ATM might include ANE1, as the frequency of this rare disorder might be underestimated.

Keywords Acute necrotizing encephalopathy · Spinal cord injury · Transverse myelopathy · Transverse myelitis · Acute disseminating encephalomyelitis

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Introduction

Acute transverse myelitis (ATM) is a rare cause of non-traumatic spinal cord injury (ntSCI) comprising a heterogeneous group of immune-mediated diseases. The typical clinical presentation is a non-traumatic paraplegia with an acute (frequently within hours) onset. The first documented use of the term "acute transverse myelitis" was by Miller and Ross in 1931, describing a case of acute quadriplegia in a child following measles with complete regaining of function on later follow-up [1]. Following this initial report, several publications focused on the topic of transverse myelitis—mainly in cases of acute post-vaccination or parainfectious paraplegia. These publications predominantly derived from pediatric cases where ATM occurred after viral diseases (like rubella or measles). The diagnostic term ATM was clinically applied in a rather descriptive manner, while in many cases the definite etiology remained unclear.

Eventually, more refined etiological mechanisms of ATM were introduced, based on increasing knowledge in neuro-immunology and improvements in neuro-imaging (i.e. magnetic resonance imaging [MRI]). These methods are sensitive to distinguish different clinical entities (or disorders), thus improving the diagnostic yield [2–6]. ATM

was classified as a neurological syndrome based on immuno-reactive pathomechanisms with a typically acute or sub-acute onset. Today for diagnosing ATM, the proof of a neuro-immunological pathomechanism is required by either a positive cerebrospinal fluid (CSF) (pleozytosis or positive immunoglobulin index), or by defined MRI suggestive for central nervous system (CNS) inflammation (MRI of the entire neuro-axis including gadolinium administration) [5, 7, 8]. In contrast to ATM, the term "transverse myelopathy" is used rather broadly, referring to non-traumatic spinal cord lesions in general [6, 8].

We present a clinical case of ATM showing longitudinal extensive transverse myelitis, as well as thalamic involvement, that was found to carry a genetic mutation that has been recently reported to predispose to infection-triggered Acute Necrotizing Encephalopathy (ANE1) [9]. Based on this rare case of a genetically triggered ATM, we propose a refined diagnostic algorithm including this hereditary disorder in order to emphasize this potential pathomechanism in ATM. This case report has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki; a written informed consent of the patient was obtained.

Case report

Medical history

In January 1999, a 36-year-old woman was admitted with an acute onset of an incomplete quadriplegia (American Spinal Injury Association [ASIA] impairment scale C, level C4) and a defined perioral hypoesthesia around the mouth (dermatomes innervated by the long projecting trigeminal spinal roots).

The sensory-motor deficits occurred rapidly within 24 h, 3 days after the onset of unspecific infectious symptoms of the upper respiratory tract with coughing and fever (39.5 °C). Prior to this episode, her health was unremarkable and she had never suffered from any neurological or other systemic disorder. Similar infectious symptoms had occurred to her in the past, but they had rarely been accompanied by fever.

Diagnostic workup

Clinical presentation

Glasgow coma scale (GCS) was 15/15 points; other than a mild perioral hypoesthesia, the cranial nerves were intact. Tendon reflexes were abolished except for biceps reflexes, which were symmetrically weak. Babinski sign was negative and muscle tone was hypotonic. Motor level was at C5, sensory level at C4, both at left and right side symmetrically. Severe paresis affected all muscles of the lower and upper limbs, inducing a total loss of her walking ability and a severely impaired upper limb function (total ASIA motor score 38/100). Below the level of lesion at C4, aesthesia and algesia were incompletely impaired. There was hypoesthesia and hypalgesia in the sacral dermatomes, bulbocavernosus reflex was negative and there was no voluntary sphincter contraction, or voluntary urinary voiding. Respiratory and cardiac functions were unremarkable, skin showed no noticeable alterations.

Laboratory workup

The initial cerebrospinal fluid (CSF) analysis showed a normal cell count (0.3/µl, leukocytes), but increased protein levels (0.79 g/l). Oligoclonal bands (OCB) were negative and a blood-CSF barrier disturbance was found (albumin quotient 19.7, IgG quotient 0.44) without intrathecal synthesis of immunoglobulins. A second CSF analysis revealed a pleocytosis of 19 cells per µl consisting mostly of monocytes, while blood-CSF-barrier was still impaired.

Blood exams showed normal cell counts, erythrocytes sedimentation rate of 3 mm/h, normal C-reactive protein and no liver or renal dysfunction. The screening for immunological disorders was negative (RF, ANA, ANCA, anti-ds-DNA, SSA/SSB). Vitamin B12 was at normal level.

No specific viral or bacterial infection was found in the blood or the CSF (cytomegalovirus, adenoviruses, Epstein-Barr virus, varicella zoster virus, herpes simplex virus I + II, coxsackie virus, HIV, treponema pallidum, borreliosis, leptospirosis, mycobacteria, aspergillum, brucellosis, chlamydia, bartonellosis, campylobacter, salmonella, legionella). The pulmonal or bronchial infection causing the initial fever could not be specified.

NMO-(aquaporine-4)-antibodies were not for routine diagnostics at that time (1999), and therefore were not investigated initially. However, at follow-up analysis, NMO-antibodies in 2012 were negative.

Neuroimaging

The MRI of the spine showed an extensive myelopathy ranging from C2-Th1 and a second myelopathic area at the conus medullaris that were suggestive for an extensive inflammation (see Fig. 1). Brain MRI revealed several symmetrical lesions of the anterior thalamus, within the pons and the medulla oblongata (see Fig. 2). There were no findings suggestive for vascular or tumor disorders.

Electrophysiology

Electrophysiology showed initially severe axonal lesions in the upper limb nerves with normal nerve conduction

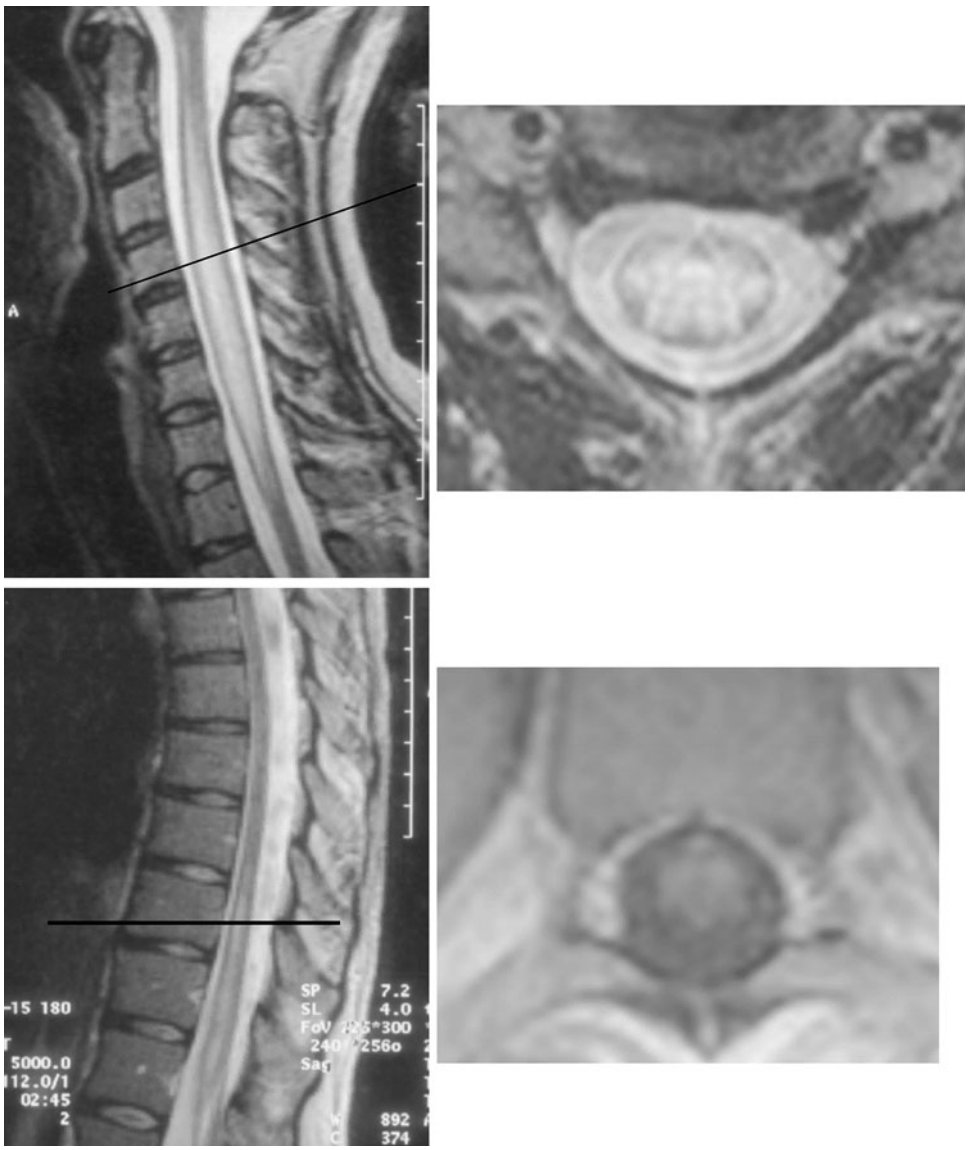

Fig. 1 MRI 2 days after onset of symptoms: extensive lesion of the cervical spine and the conus medullaris

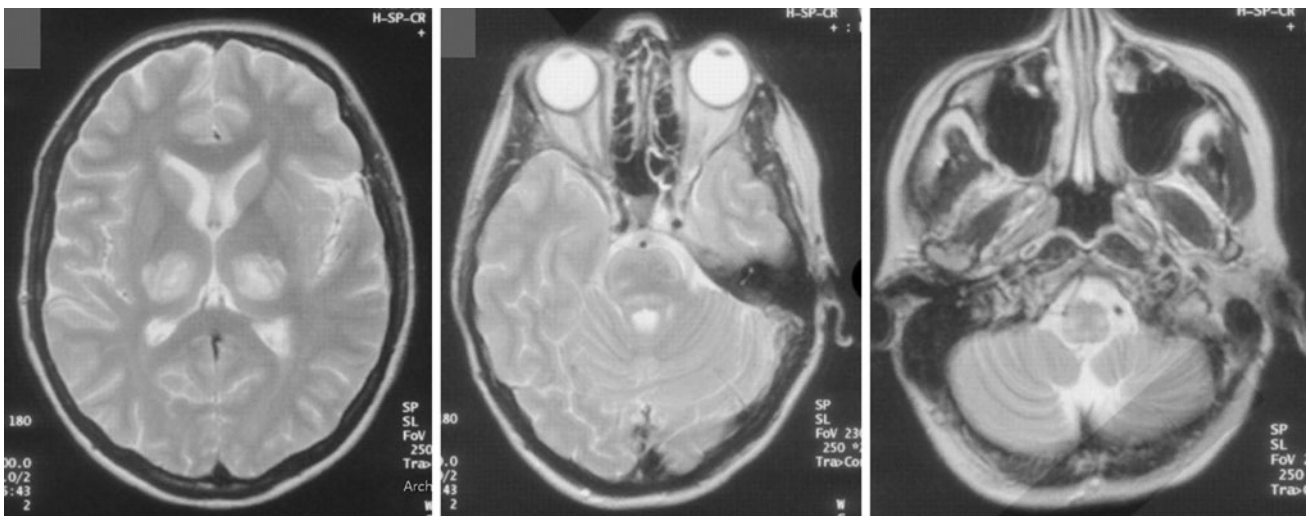

Fig. 2 MRI 2 days after onset of symptoms: lesion in the thalamus, pons and medulla oblongata

velocity and loss of F-waves. Nerve conduction studies of the tibial nerves showed normal amplitudes, conduction velocities and F-wave latencies. The results were atypical for Guillain–Barre Syndrome (GBS), but indicated a severe axonal loss due to the intramedullar lesion of the anterior horn cells in the cervical spine. Measurements after 4 weeks showed a reduction of amplitudes (40 %) in the tibial nerves and prolongation of F-wave latencies (60 ms). At 5 months, amplitudes of the upper limb nerves recovered slightly (max 2.6 mV), whereas amplitudes of the lower limb nerves remained normal (9 mV/17 mV). F-wave latencies recovered to slight impaired values in the upper limbs (28–30 ms ulnar nerves, 30–35 ms median nerves) and to normal values in the lower limbs (54–55 ms tibial nerves).

Treatment and course

Steroid therapy (Dexamethasone orally 4 × 4 mg/day for 8 days and consecutive reduction) was empirically initiated. Within 1 month, the signal-alterations on the MRI of the central nervous system were reduced—small lasting alterations were found in the thalamus, the cervical spine and in the conus medullaris—matching the clinical improvements.

In the following, the patient regained sensibility and reflexes, motor deficits improved slowly and she regained walking-ability with crutches and independency from assistance within 5 months. Bladder and bowel deficiency restored to a fully normal function. After discharge, she improved further to an almost normal gait (no walking aids required, walking distance unlimited but slightly reduced speed). Follow-up MRI showed persistent minor myelopathy in the cervical spinal cord and symmetric residual T2-hyperintense lesions in the thalamus (see Fig. 3). No new T2-hyperintense lesions occurred. Since 1999, the patient did not experience any additional episode of an acute CNS impairment.

Family history

The patient presented above is born in Switzerland as one of seven children (see pedigree, Fig. 4). Her mother derives from a large family with a total of eleven siblings. One of her aunts died at young age from an unknown cause. The patient's second cousin who was born in 2000 suffered from recurrent episodes of ANE, and was as an index patient tested and found positive for a missense mutation on the RANBP2 gene on chromosome 2q12.1–2q13 in 2007 [9]. The father of this child, the patient's first cousin, was tested positive for the mutation as well, without any prior or later history of infection-triggered encephalopathy. Another first cousin born in 1958 is reported to have suffered from acute cerebral disorder (non-traumatic coma in childhood) with consecutive residual mental retardation. This cousin's caretaker refused the genetic testing.

The present patient was found to carry the missense mutation associated with ANE1 as well [9].

Discussion

The understanding of ATM has continuously improved over the last decades, and comprises various mainly immune-mediated myelopathies. Accordingly, definitions and diagnostic criteria will have to be adjusted as further insights in pathology and course of disorders are revealed.

Acute transverse myelitis: definitions and epidemiology

ATM is clinically recognized by an acute to subacute development of a paraparesis or paraplegia with a maximum of deficits within 4 h up to 21 days [6]. While signs of CNS or systemic inflammation (CSF pleocytosis, IgG-elevation, MRI gadolinium enhancement) [5, 6, 8, 10] are

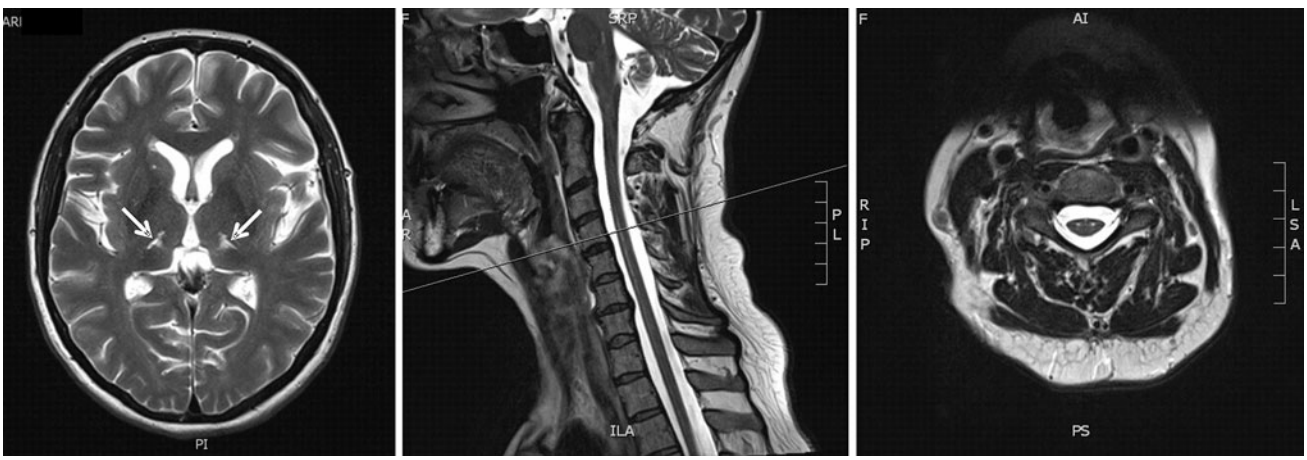

Fig. 3 MRI 2012: residual lesions in thalamus (*arrows*) and cervical spinal cord

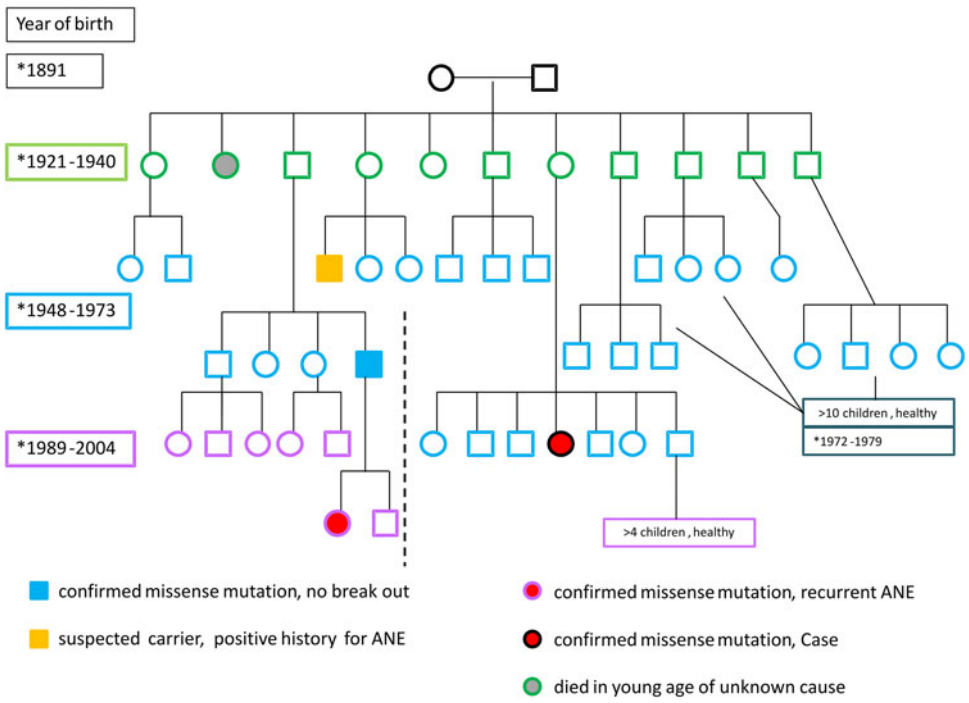

Fig. 4 Pedigree

key findings, other causes (e.g. vascular disorders, tumors, degeneration) need to be excluded. Severity of symptoms, extent of inflammation, time and slope of symptoms may hint towards the etiology or potential differential-diagnosis [5, 8, 11]. After repeated exclusion of up-to-date known causes for ATM, idiopathic ATM might be diagnosed according to the Transverse Myelitis Consortium Group (TMCG). [5].

Due to continuous changes in criteria and definition of ATM, epidemiological studies are hardly comparable. An early study targeting the incidence of ATM in adults was done from 1955 to 1975 in Israel by Berman et al. [3], stating an annual incidence of 1.34 per million per year. Estimates in other studies even range to 31 per million per year, depending on definition and inclusion criteria (e.g. ATM in MS/NMO/systemic diseases (SD), definition by ICD10) [4, 12, 13]. Although ATM can manifest at any age, three peaks are described at the age of 0–5, 10–19 and 30–39 years [3, 4, 14, 15].

The differential diagnosis in ATM

The challenge in the diagnosis of ATM lies in a comprehensive and timely diagnostic workup (Fig. 5) for as in the majority of disorders, advising appropriate treatments and early interventions are assumed to be important for improved outcomes.

Neuro-immunological disorders (i.e. multiple sclerosis [MS], neuromyelitis optica [NMO]) represent the most frequent cause of ATM, as has been shown in a large multicentre ATM-cohort study (seven centers, spinal cord infarct excluded; $n = 234$: MS 13.3 % and NMO 20.9 % resp.) [16]. The McDonald criteria define four areas within the CNS that are most commonly affected by MS: periventricular, infratentorial and juxtacortical region and the spinal cord [17]. In general, ATM as a symptom of clinically definite MS occurs rather rare (in about 0–11 % of adult MS patients [18]). The conversion rate of isolated *complete ATM* into clinically definite MS is estimated at less than 2 % per 5 years [19]. Risk factors for the later development of MS are the extent of inflammation (rather partial), positive OCB or abnormal brain MRI (if not yet fulfilling MS criteria) [11, 20, 21]. *Partial ATM* is, in contrast to complete ATM, much more likely to be a symptom of MS [22]: the conversion rate into clinical definite MS ranges between 20–30 % over 5 years [19], while Cordonnier et al. [21] even stated a conversion rate of 57.7 %. NMO (also called Devic syndrome), rather recently, is considered a separate entity from MS. NMO is defined by the combination of longitudinal extensive transverse myelitis (LETM) and optical neuritis [23]. Since aquaporin-4-Ab were found to be associated with this disease, the distinction from MS is now widely accepted. OCB are typically not found and the myelitis is required to involve the height of three vertebral segments. Patients with isolated LETM are at high risk to develop NMO or relapsing LETM if NMO-Ab are positive [24, 25].

Systemic immunologically mediated diseases have been shown to be the second largest subgroup of diseases causing ATM (25.1 %, $n = 234$) [16]. Sjögren's syndrome was most often diagnosed (28 cases, 12 %) followed by sarcoidosis (17 cases, 7.2 %) followed by

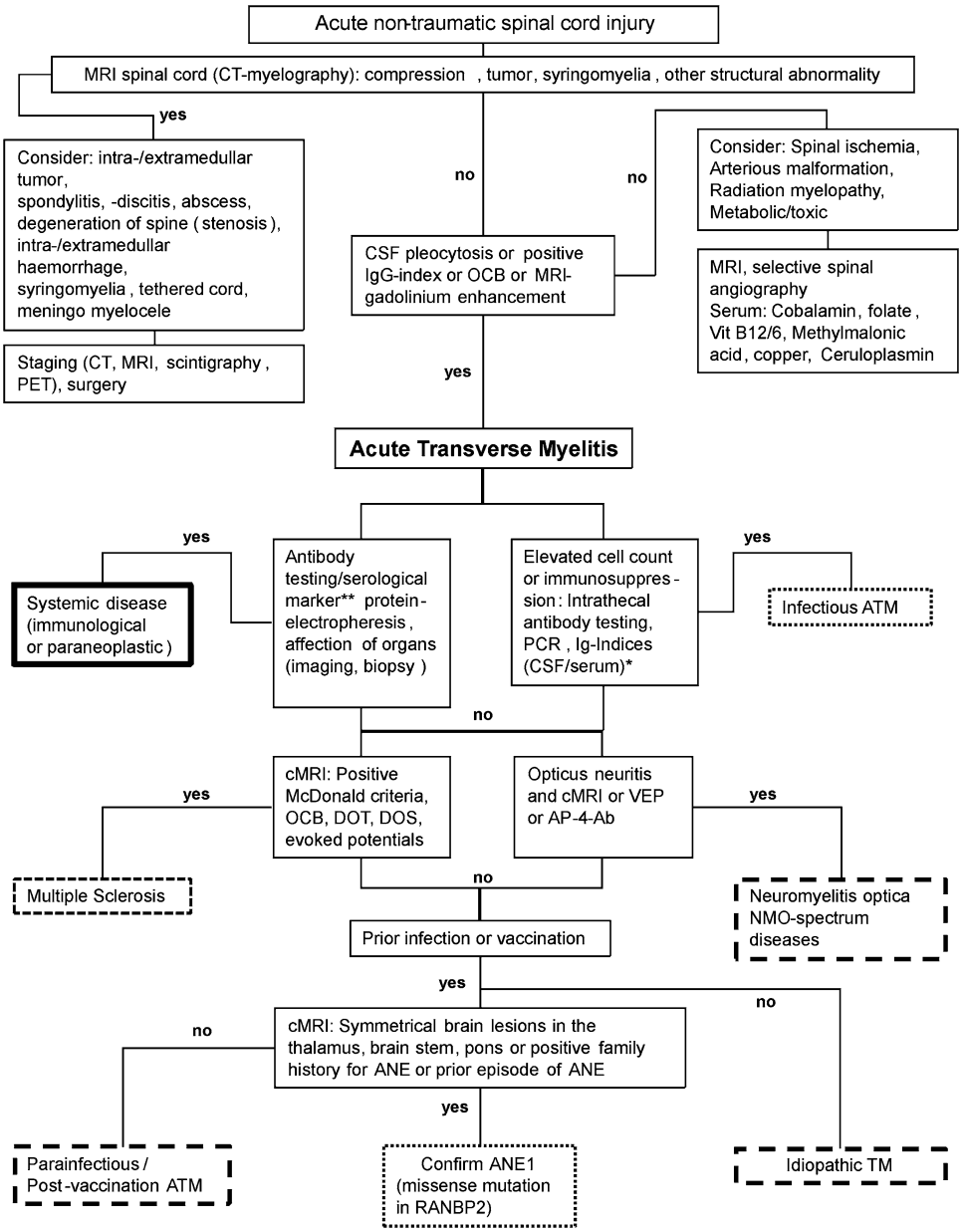

Fig. 5 Proposed diagnostic scheme. *ATM* acute transverse myelitis, *ANE* acute necrotizing encephalopathy, *AP-4-Ab* aquaporine-4-antibodies, *cMRI* cranial magnetic resonance imaging, *CSF* cerebrospinal fluid, *DOT/S* dissemination of time/space, *NMO* neuromyelitis optica, *OCB* oligoclonal bands. *Mycoplasma, treponema pallidum, borreliosis, mycobacterium tuberculosis, chlamydia, brucellosis, cocksackievirus, HTLV; VZV; HIV; HHV1 + 2, CMV, EBV, adenovirus, HCV, HAV. **ANA, ANCA; ds-DNA, antiphospholipide-Ab, anti-Ro/SSA, ACE, HLA-B51 depending on clinical symptoms. *Thickness* and *shape of lines* indicates the relative frequency of disorders diagnosed in ATM: *Solid lines* > 20 %, *spaced dashed lines* 10–20 %, *dashed lines* 5–10 %, *dotted lines* < 5 %

SLE/antiphospholipide syndrome (14 cases, 6 %) [16]. In a Japanese or Turkish descent, Behçet's disease might also cause ATM [26]. Sjögren's syndrome, sarcoidosis, SLE and Behçet's disease need to be screened for by serologic markers (Anti-SSA/B, ACE, ANA + ds-DNA/anti-phospholipide-Ab, HLA-B51, respectively) complementing imaging and clinical history. Several clinical symptoms might hint to the diagnoses (e.g. sicca-syndrom, uveitis, other organ involvement (kidney, heart, lungs), mucosal ulcers, respectively) [8, 27]. Funicular myelosis or copper-deficiency related myelopathies usually present chronically, MRI reveals typically longitudinal lesions of the dorsal column, and CSF analysis might show signs of blood–brain-barrier breakdown [28, 29].

Infectious and parainfectious disorders together are reported to cause ATM in 21.4 % of cases [16]. Viral CNS infections commonly present as acute meningoencephalitis, and if the spinal cord is involved, a partial transverse myelitis is more likely [30]. True ATM caused by viral infections that are actually identified by CSF analysis are rarely reported (Coxsackie A/B Virus, Enterovirus, hepatitis A/C virus, varicella zoster virus, Epstein-Barr virus and cytomegalovirus [30–35]). Reports of ATM associated with other viral diseases (influenza, measles, rubella, polio, adenovirus) are rather heterogenic, and might be classified as parainfectious ATM [18, 36]. Bacterial or mycobacterial ATM are also rarely reported: mycoplasma pneumonia (37 cases), schistosomiasis (one case) [36], brucellosis

infections (20 cases) [37, 38], two cases of *chlamydia psittaci* [39] and four cases of documented Lyme neuroborelliosis [40]. Although neurosyphilis presents mainly as chronic myelopathy, there are two reported cases of ATM [41]. Comparably tuberculosis shows a rather chronic progression, but in rare cases neurological presentation can manifest as ATM (three cases) [42]. A larger percentage of ATM is assumed to be parainfectious and it is defined by a prior history of a mostly viral infection. Vaccine-associated ATM contributes to this subgroup although post-vaccination ATM is rare [18].

Idiopathic ATM is considered a diagnosis by exclusion and exact definitions remain unclear. The TMCG was the first to assess specific criteria and an exclusion of prior infections or vaccinations is not uniformly required [5]. Accordingly, a recent retrospective analysis in children applying the TMCG criteria did not differentiate parainfectious from idiopathic ATM [43], while De Seze et al. and Borchert et al. excluded parainfectious ATM [16, 18]. An Intergroup correlation addressing a group difference between idiopathic and parainfectious ATM is not published. The outcome of idiopathic ATM according to TMCG criteria was retrospectively investigated by de Seze et al. [16]: The subgroup of idiopathic ATM was shown to be heterogeneous in terms of clinical presentations, extent of spinal lesion and outcome, and criteria for outcome prediction could not be identified.

A comparable parainfectious pathophysiological mechanism is considered in acute disseminated encephalomyelitis (ADEM), as mentioned by Al Deeb et al. in 1997 [44]. The diagnosis of ADEM calls for a monophasic inflammatory demyelinating disease that can, but does not need to, be associated with acute viral infection or vaccination [45]. Typical clinical presentation is acute, multifocal and poly-symptomatic (meningomyeloencephalitis), and CNS involvement can include inflammation of the spinal cord [45]. Neuroimaging reveals non-MS typical lesions (e.g. deep grey matter involvement, sparing of periventricular white matter), but a reliable distinction to MS and NMO can be difficult [46].

Intramedullary tumors should be excluded by spinal MRI, although in some cases associated edema and gadolinium enhancements might be challenging [47]. Paraneoplastic disorders might cause subacute myelopathy, e.g. the small cell lung carcinoma and related autoimmunities [48] or neurochemical toxicity [47].

Transverse myelitis and ANE1

The acute necrotizing encephalopathy (ANE) is an acute and severe parainfectious CNS disease rarely diagnosed in adult neurology. It is known as a disease of childhood, first described in 1965 [49] and later on reported in mostly Japanese children in the 90s [50]. By now, it is known that this form of acute encephalopathy in children occurs worldwide [51, 52]. Since 2000, few cases on ANE in adults have been reported [53–57].

ANE is defined by a rapid progressive encephalopathy after a common viral infection as influenza or parainfluenza [50]. The criteria of ANE require exclusion of direct viral or bacterial infection of the CNS [58]. The MRI shows multiple lesions of the CNS: typically symmetrical lesions of the thalami, pons and brain stem [59]. Elevated liver enzymes contribute to the diagnosis [59]. The pathophysiological mechanisms are not known. It is supposed that the encephalopathy and the neuronal damage and necrosis is mediated by the specific effect of an excessive cytokine release in the CSF [60]. Some patients with ANE showed a dramatic response to early high–dose steroids [61].

While ANE usually occurs sporadically, few cases of recurrent and/or familial episodes suggesting an inherited disposition have been reported [62]. In 2009, a genetic disorder with incomplete autosomal-dominant trait was reported: a missense mutation in the gene coding for the nuclear pore Ran Binding Protein 2 (RANBP2, OMIM*601181) on chromosome 2q was found to transmit a predisposition for familial ANE (=ANE1) in European, Asian and African families [9, 63]. Among the familial cases, the formation of CNS lesions was found to be more disseminated than originally described for ANE, including spinal cord lesions. In addition, not only children but also adolescents and one adult (described herein) were observed to be affected [9]. No patient with ANE1 showed elevated liver enzymes, in contrast to ANE. Importantly, the missense mutation leading to ANE1 was shown to be distinguished from MS, since there was no such mutation found within a representative collective of MS-patients [9]. ANE1, according to Neilson et al. and Bergamino et al., should be considered if criteria for ANE and any of the following are met: (I) familial history of neurological symptoms, might be parainfectious, (II) recurrent encephalopathy following fever, (III) additional MRI changes in one of the following: medial temporal lobes, insular cortices, claustrum, external capsule, amygdale, hippocampi, mammillary bodies, and spinal cord [64].

The missense mutation in the RANBP2-gene and its actual function within the pathological mechanisms of ANE1 are not yet entirely understood. It transmits an increased vulnerability for developing an episode of ANE1 triggered by a variety of mostly viral infections [9]. Many different molecular possibilities are discussed [9], but one trait that is already known for other diseases offers a plausible explanation: The protein is known to play a role in the energy metabolism of neuronal cells [65, 66]. Hence, one theory is that a malfunction of the RANBP2 nuclear pore leads to an energy breakdown when the cell mechanisms are

challenged by an acute infection [9]. Similar mechanisms are already assumed for other infection mediated encephalopathy-syndromes such as Reye's (like) syndrome (Mitochondriopathy caused by different enzymatic deficiencies [67]), Wernicke Encephalopathy (hypovitaminosis inducing lack of glucose catabolism and deficit in mitochondrial metabolism [68]) or—genetically determined—Leigh Syndrome (mitochondrial disease [69]).

Summary and conclusion

Our patient represents a very rare case of an ANE1-associated ATM that presented with an acute quadriplegia. The patient met the criteria for ANE1 with typical radiological features, positive family history and a proven missense mutation in the RANBP2-gene. The sudden onset after an infection (3 days) and symmetrical T2-hyperintense cerebral (thalamus and pons) lesions are typical findings in ANE1, although involvement of the spinal cord has been reported in only three cases [9]. The favorable outcome might be due to the steroid treatment, as steroid responsiveness is known for ANE [64]. This case emphasizes the diagnostic challenges in ATM, and a diagnostic algorithm is proposed to guide a timely and comprehensive work up for introducing appropriate treatments (Fig. 5).

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Conflicts of interest The authors declare no conflict of interest.

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