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Short Communication

A case of longitudinally extensive transverse myelitis following vaccination against Covid-19

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ABSTRACT

Background: Longitudinally extensive transverse myelitis (LETM) is a rare subtype of transverse myelitis (TM) that potentially results in relevant disability. Apart from association to neuromyelitis optica and other chronic demyelinating diseases of the central nervous system, many other aetiologies are known. Particularly systemic infections and vaccination are considered potential triggers for immune mediated inflammation of the spinal cord. In the course of the current Covid-19 pandemic several cases of TM following Covid-19 infection have been described. Here we present a case of LETM following vaccination against Covid-19 with AZD1222, AstraZeneca. An extensive diagnostic work up was performed to rule out alternative causes, including prior and current Covid-19 infection.

Conclusion: To our knowledge this is first case of LETM possibly related to Covid-19 vaccination that is published after marketing authorisation of various vaccine candidates.

1. Introduction

Longitudinally extensive transverse myelitis (LETM) is a rare subtype of transverse myelitis (TM) extending three or more consequent vertebral segments (Wingerchuk and Weinshenker, 2013). As the condition often results in relevant disability, a rapid and systematic diagnostic work up is necessary to identify the particular aetiology in order to initiate appropriate treatment as soon as possible. LETM can be part of NMOSD, multiple sclerosis and other autoimmune diseases, but many other aetiologies have to be considered as well (Kitley et al., 2012). Myelitis in general most commonly is induced by direct infection or para- and post-infectious autoimmune mediated inflammation (Agmon-Levin et al., 2009; Karussis and Petrou, 2014; Transverse Myelitis Consortium Working Group, 2002; West et al., 2012). In a similar manner various environmental factors have been regarded as a comparable trigger for autoimmune myelitis, particularly vaccination (Agmon-Levin et al., 2009; Karussis and Petrou, 2014). Here we present a case of LETM following the first dose of Covid-19 vaccination with AZD1222, AstraZeneca.

2. Case presentation

A 45-year-old male was admitted to our emergency ward with poor general condition, thoracic back pain and urinary retention. Apart from an atopic dermatitis, which did not require immunotherapy, there was no significant comorbidity. Eleven days before admission he had received the first dose of Covid-19-Vaccine (AZD1222, AstraZeneca) followed by an episode of chills, fever, headache and tiredness for two days. After initial improvement, symptoms worsened again on day eight with chills, new onset of headache, thoracic back pain and general weakness.

In the initial neurologic examination no motor or sensory dysfunction could be objectified, though urinary retention required catheter insertion. There was no fever or other signs of systemic infection. Nasopharyngeal swab was negative for SARS-CoV-2-RT-PCR. Within one day after admission the patient developed an acute flaccid tetraparesis, emphasizing lower limbs, and a sensory level at Th9.

MRI revealed a LETM lesion showing T2 hyperintense signal of the spinal cord with wide axial and longitudinal extent reaching from C3 to Th2 without gadolinium enhancement (Fig. 1A). A brain MRI was normal. CSF analysis showed a predominantly polymorphonuclear pleocytosis of 481 cells/µl (67% granulocytes), increased protein (1,4 g/

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l), increased lactate (3,98 mmol/l) and decreased glucose (CSF/serum ratio 0,43). There was no evidence of intrathecal Ig-synthesis or unique oligoclonal bands in CSF.

The patient immediately received a calculated anti-infective combination therapy with acyclovir, ceftriaxone and ampicilline and additionally an anti-oedematous medication with 100 mg prednisolone iv. Bacterial culture of CSF and blood was negative. A further extensive pathogen diagnostic proved negative for all agents tested, including cryptococcus, escherichia coli, listeria monocytogenes, neisseria meningitidis, parechovirus, streptococcus agalactiae, streptococcus pneumonia, haemophilus influenza, HSV1/2, VZV, HHV-6, CMV, EBV, tick-borne encephalitis, neuroborreliosis, ECHO, enteroviridae, coxsackie, west nile virus, mycoplasma, tuberculosis, syphilis, HIV, hepatitis B and hepatitis C. As soon as a specific infection of the spinal cord was excluded, a pulse treatment with high dose corticosteroids was initiated applying 1 g methylprednisolone per day for five consecutive days followed by oral tapering.

Further work up included laboratory screening for vasculitis and connective tissue disease without pathological signals. There was no evidence of vitamin B12 deficiency. Aquaporin-4- and MOG-antibodies were negative in serum and CSF. Moreover, there was no further findings consistent with multiple sclerosis, NMOSD, MOG-associated disease or ADEM as cerebral MRI and VEP were normal. A panel diagnostic for anti-neuronal autoantibodies in CSF was negative, containing antibody testing against Hu, Ri, ANNA-3, Yo, Tr, Myelin, Ma/Ta, GAD65, Amphiphysin, glutamate receptors of type NMDA and AMPA, GABA-a-receptor, GABA-b-receptor, LGI1, CASPR2, ZIC4, DPPX, Glycin-receptor, mGluR1, mGluR5, GluRD2, Rho GTPase, ITPR1, CARPVIII, Homer 3, Revoverin, Neurochondrin, Flotillin, and IgLON5.

Finally, a positive SARS-CoV-2-IgG serum antibody was detected. As the available in-house assay uses ELISA-testing against spike protein antigen it is not possible to distinguish antibody response to prior infection from response to vaccination. We additionally ordered an external immunoassay testing for IgG-antibody response against nucleocapsid antigen, which turned out negative. There was no current signs or history of symptoms suspicious for Covid-19, especially no respiratory symptoms, anosmia or ageusia. Throughout hospital treatment RT-PCR-testing for SARS-CoV-2-RNA was repeatedly negative in several nasopharyngeal swabs. Furthermore, RT-PCR for SARS-CoV-2-RNA as well as SARS-CoV-2-antibody was negative in CSF.

Symptoms rapidly improved after initiation of high dose corticoid therapy, especially tetraparesis and sensory level receded, urinary catheter could be removed. Follow-up CSF examination on day 7 showed a significant reduction of cell count, now transformed to a mononuclear profile (76 cells/µl, 100% lymphocytes), lactate decreased, protein and glucose normalized. MRI provided concordant results showing decline in axial and longitudinal extent of T2 hyperintense spine signal (Fig. 1B).

When discharged from hospital on day 16 the patient walked independently, showed residual mild paresis of distal finger flexors and dorsiflexion of the toes, intermittent paraesthesia in feet and a slightly impaired bowel and bladder emptying. An oral corticoid tapering scheme and a rehabilitation treatment were determined.

3. Discussion

In the course of the current Covid-19 pandemic a growing number of neurological manifestations and complications have been described. Whereas data so far indicate that clinical impact of direct infection of the nervous system by SARS-CoV-2 is less common, rather immune mediated inflammation is considered the main cause of neurological involvement (Ellul et al., 2020; Roy et al., 2021). In this context an increasing number of reports on spinal cord affection and TM associated to Covid-19 have been published since 2020 (Artemiadis et al., 2021; Chow et al., 2020; Garg et al., 2021; Jumah et al., 2021; Kilbertus, 2021; Moreno-Escobar et al., 2021; Munz et al., 2020; Shahali et al., 2021). Most cases represent post-infectious immune mediated myelitis, only few are considered para-infectious or infectious (Artemiadis et al., 2021).

On the other hand, onset of myelitis temporally associated to vaccination has repeatedly been observed. Various cases of myelitis have been described following different vaccines (Agmon-Levin et al., 2009; Akkad et al., 2010; Karussis and Petrou, 2014). Particularly regarding Covid-19 vaccines a case of transverse myelitis has been reported during pre-approval clinical trial for AZD1222 (AstraZeneca),

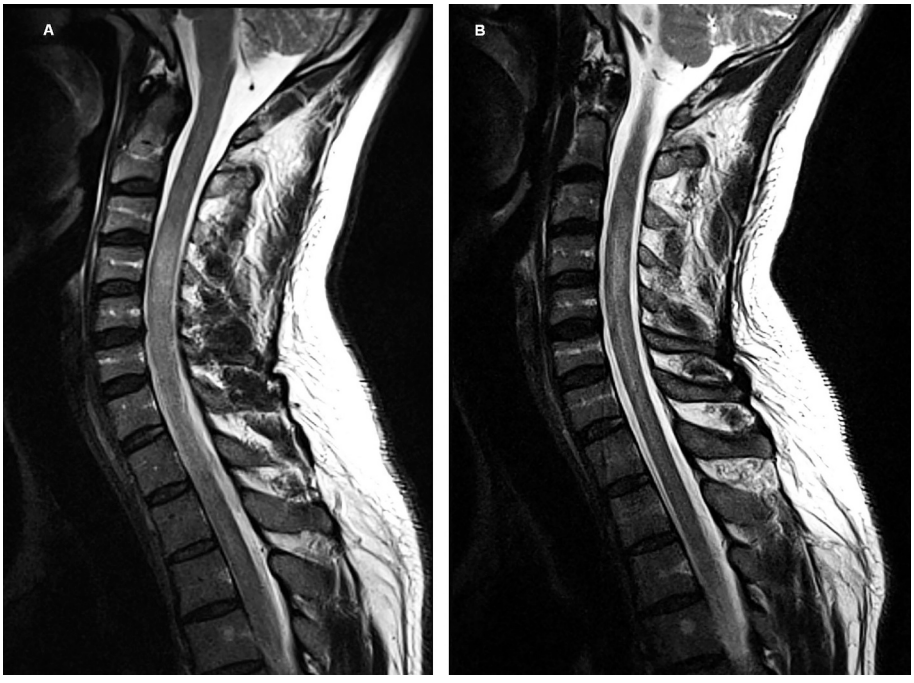

Fig. 1. Spinal cord MRI: (A) sagittal T2 weighted image of cervicothoracic spine shows hyperintense signal with wide axial and longitudinal extent. (B) Follow-up MRI after 8 days shows decline of T2 hyperintensity in axial and longitudinal extent.

where myelitis developed 14 days after booster vaccination and was finally estimated as possibly related to the vaccine. In contrast, for two other cases of transverse myelitis that also occurred during clinical trials a relation to AZD1222 was denied (one pre-existing multiple sclerosis, one in the control-group receiving meningococcal vaccine) (Medicines and Healthcare products Regulatory Agency (MHRA), 2021a; Voysey et al., 2021). Recently a single case of focal myelitis following Covid-19 vaccination with AstraZeneca-vaccine in India has been described (Singh Malhotra et al., 2021). Moreover, national vigilance boards already received several spontaneous reports on myelitis following covid-19 vaccines, for instance in the UK 17 cases for BioNTech vaccine and 45 cases for AstraZeneca vaccine (as at 28-Apr-2021), in Germany one case for BioNTech vaccine and 2 cases for AstraZecena vaccine (as at 30-Apr-2021) and in the US 9 cases without mentioning specific vaccine (as at 02-Mar-2021) (Goss et al., 2021; Medicines and Healthcare products Regulatory Agency (MHRA), 2021b, 2021c; Paul-Ehrlich-Institut (PEI), 2021). However, no further data on diagnostic findings is available and generally no distinction is made between infectious and other aetiology. Hence, the implication of these spontaneous reports remains vague and assessment of potential causality is not possible.

The case of LETM presented here shows a close temporal association to Covid-19 vaccination, as symptoms occurred within 11 days post injection of first dose AZD1222, AstraZeneca. A very extensive diagnostic work up has been performed to rule out alternative diagnoses. Particularly CSF findings of high cell count and predominant granulocytes initially suggested an infectious aetiology and triggered short term anti-infectious treatment. Yet, no pathogen was detected and CSF as well as clinical symptoms finally improved under immunosuppressive therapy with corticoids, confirming aseptic inflammation. Although uncommon, neutrophil pleocytosis of high cellularity and elevated lactate are also known to be present in highly active phases of autoimmune CNS disorders such as NMOSD (Jarius et al., 2011; Pfeuffer et al., 2017). The rapid and dramatic recovering of CSF profile and clinical symptoms as seen in our patient still is consistent with inflammatory reaction rather than myelitis associated to NMOSD.

Special attention had to be made for the detection of a positive SARS-CoV-2-IgG serum antibody in our patient's blood. Nevertheless, apart from a negative history of Covid symptoms, especially the constellation of low-level IgG-response to spike protein antigen alone and negative results for nucleocapsid-directed antibodies strongly argues against prior infection und rather indicates emerging response to vaccination. The date of antibody detection 13 days post vaccination is consistent with findings in serology studies that showed a relevant SARS-CoV-2-IgG-reponse directed against spike protein at day 14 after prime dose of AstraZeneca-Vaccine (Folegatti et al., 2020). In conclusion a post-infectious immune mediated inflammation following Covid-19 appears highly unlikely.

4. Conclusion

To our knowledge this is first case of LETM possibly related to Covid-19 vaccination that is published after authorisation of various vaccine candidates. So far mainly reports on post- and para-infectious aetiology of myelitis related to Covid-19 have been released. In the nearest future a further rising of both global Covid-19 infection rates and vaccination rates can be expected. During the ongoing pandemic both instances have to be considered as possible triggers, when diagnostic work up of myelitis or other immune mediated condition is performed. In certain cases, specific serological approaches are necessary to reasonably distinguish antibody response to prior Covid infection from response to vaccination.

As the neurologic impact of the Covid-19 pandemic keeps growing, apparently vaccine related disorders might need to be added. Certainly, more data is needed for a better judgement of the actual relevance and potential risk. The rarity of such an occurrence should currently not deter the use of vaccines, since global vaccination represents the most important strategy to fight this pandemic.

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