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Case report

Aggregatibacter aphrophilus ventriculitis following C1-C2 transarticular screw fixation

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ABSTRACT

Objective: Central nervous system (CNS) infections after cervical spine surgery are a rare but serious complication and may be caused by uncommon pathogens. We report the case of a 57-year-old male who developed slowly progressive mental confusion with headaches, increased daytime sleepiness and mild gait disturbance within the last 3 weeks. Six weeks prior to admission to our department, he underwent an atlantoaxial fusion by C1-C2 transarticular screw fixation for rheumatoid arthritis related C1-C2 multidirectional instability.

Methods: We analyzed clinical and neuroradiological findings.

Results: The findings were consistent with communicating hydrocephalus secondary to ventriculitis and the left C1-C2 screw was found to be misplaced with perforation of the dura. The situation was interpreted as implant related surgical site infection of the cerebrospinal fluid followed by ventriculitis and hydrocephalus. Bacterial broad range 16S rRNA gene PCR from the cerebrospinal fluid (CSF) followed by sequencing identified *Aggregatibacter aphrophilus* as the causative agent, while conventional cultures remained negative due to its fastidious growth. The patient was successfully treated with a lumbar drain and intravenous ceftriaxone.

Conclusions: To our knowledge, this is the first report of *Aggregatibacter aphrophilus* ventriculitis following C1-C2 transarticular screw fixation.

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Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; IE, infective endocarditis; RA, rheumatoid arthritis; NSAIDS, non-steroidal anti-inflammatory drugs; MRI, magnetic resonance imaging; NECCT, non-enhanced cranial computed tomography; GCS, Glasgow Coma Scale; MTX, methotrexate; SSI, surgical site infection.

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1. Introduction

Ventriculitis is an inflammation of the ependymal lining of the cerebrospinal fluid (CSF) containing ventricular system of the brain. Causes of bacterial ventriculitis include previous head trauma, indwelling ventricular catheters, ruptured brain abscesses, meningitis, and previous ventricular surgery – common bacterial pathogens are *Streptococcus* and *Staphylococcus* species as well as gram-negative rods [1–3]. Clinical features of ventriculitis comprise headaches, fever, signs of meningitis, seizures, and hydrocephalus either due to occlusion of the aquaeduct of Sylvius or the foramina of Luschkae and Magendii or due to impairment of CSF resorption [1,4].

Aggregatibacter aphrophilus was formerly called *Haemophilus aphrophilus* or *H. paraphrophilus* and is a member of the HACEK group; a group of Gram-negative bacteria historically known for difficult-to culture pathogens causing infective endocarditis (IE) [5]. The Gram-negative coccobacillus is a member of the oropharyngeal flora. Besides IE, *A. aphrophilus* is associated with brain abscesses, bone and joint infections and endophthalmitis [6]. Two case reports of ventriculitis due to *A. aphrophilus* can be found in the literature. Both were cardiogenic in origin, including a case of pyogenic ventriculitis following infective endocarditis [7] treated with ceftriaxone, metronidazole and vancomycin; and a case of ventriculitis in a 22-year old patient with a cardiac right-to-left shunt treated with ceftriaxone, metronidazole, vancomycin and intrathecal gentamicin [8].

2. Materials and methods

A 57-year-old male was referred to our neurosurgery department after he syncopized twice at a local airport and was found disoriented by the airport-police. According to the history given by the next of kin, he developed slowly progressive mental confusion with headaches, increased daytime sleepiness and mild gait disturbance within the last 3 weeks. The patient's past medical history was positive for rheumatoid arthritis (RA) on non-steroidal anti-inflammatory drugs (NSAIDS), oral steroids (prednisolone 20 mg qd po) and methotrexate (MTX, 20 mg qw sc), arterial hypertension (treated with carvedilol, spirinolactone, and valsartan) as well as chronic renal disease (GFR 32 ml/min/1.73 m^2, DD: NSAID induced). Six weeks prior to admission to our department, he underwent an atlantoaxial fusion by C1-C2 transarticular screw fixation with posterior cervical fusion (modified Gallie fusion) at an Orthopedics department in Germany. Preoperative magnetic resonance imaging (MRI) showed RA-related C1-C2 multidirectional instability with osteoligamentous compression of the myelon and beginning myelopathy (Fig. 1a and b).

On initial physical exam at our hospital (day 1), the patient was markedly confused, but had no focal neurological deficits (GCS 14). The cervical wound was adherent without signs of erythema, discharge or fluctuance. Nuchal rigidity, photophobia, Kernig's sign, and Brudzinski's sign were negative. He was hemodynamically stable and afebrile, laboratory values (CBC, electrolytes, kidney values, infectious parameters) were within normal limits except for a mild leukocytosis (10.83×10^9/L, 88% neutrophils) and elevated creatinine 1.75 mg/dl as expected. Initial non-enhanced cranial computed tomography (NECCT) (Fig. 2a–c) showed ventricular ballooning with periventricular hypodensities and an open aquaeduct of Sylvius on sagittal views (Fig. 2b). The placement of the left C1-C2 transarticular screw was found to be intraspinal with inevitable injury of dural integrity (Fig. 2c). A lumbar puncture was performed in the emergency department and revealed clear CSF at an elevated initial opening pressure of 33 cm H_2O. The CSF cell count was 270 leukocytes/μl (70% neutrophils), CSF protein was elevated at 2.7 g/L (normal range: 0.2–0.4 g/L), lactate and glucose levels were within normal ranges and the Gram stain was negative. Blood cultures were obtained, the CSF was sent for cultures and bacterial broad range 16S rRNA gene PCR analysis followed by sequencing [9]. After consultation with the Infectious Diseases department and the department of Neurology, additional diagnostic tests were obtained: peripheral blood was checked for HIV (HIV 1/2 serology and HIV-1-p24 antigen), *Treponema pallidum*, and *Borrelia burgdorferi* serologies – CSF was submitted

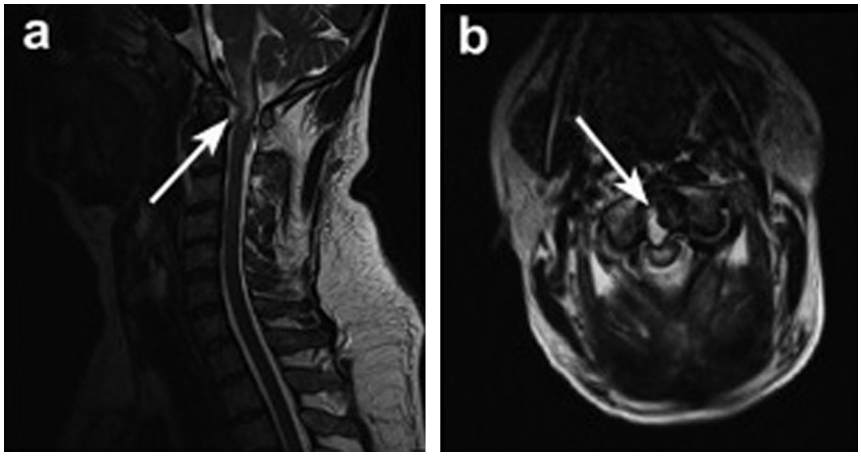

Fig. 1 – Sagittal (a) and axial (b) T2-weighted magnetic resonance imaging (MRI) views of the patient's atlanto-axial joint in the preoperative condition. The white arrows show osteoligamentous compression of the myelon and beginning myelopathy triggered by C1-C2 multidirectional instability and inflammatory changes.

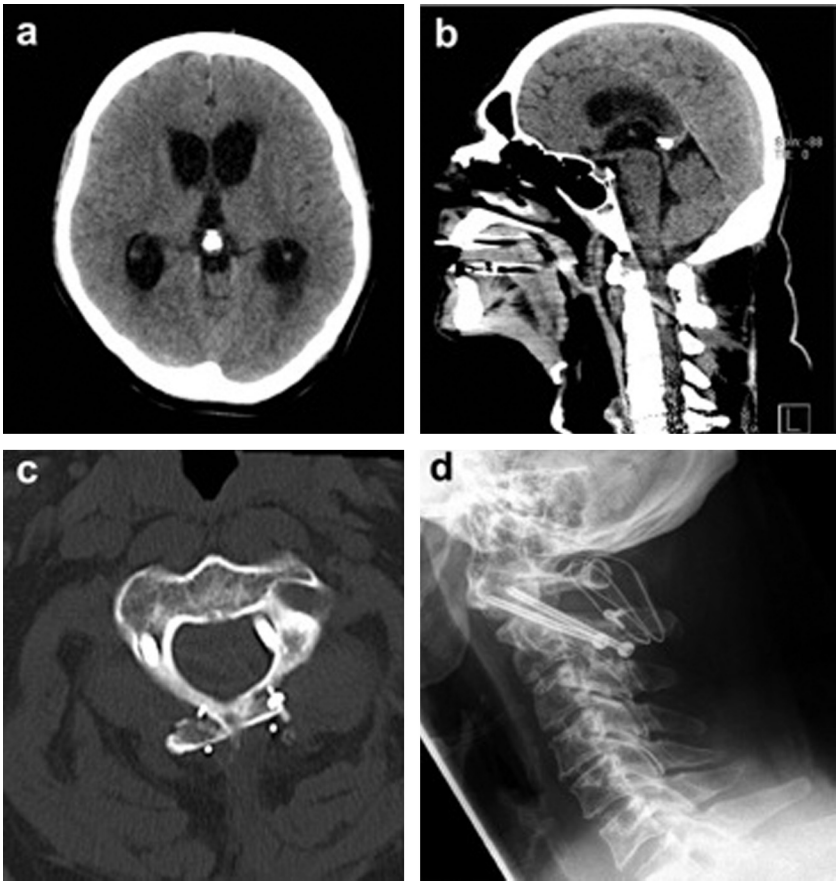

Fig. 2 – Axial (a) and sagittal (b) views as well as an axial bone window (c) of NECCT images and a plain lateral radiogram (d) on admission. Axial CT images (a) show ventricular ballooning with periventricular hypodensities and an open aquaeduct of Sylvius on sagittal views (b). The placement of the left C1-C2 transarticular screw was found to be intraspinal (c) with inevitable injury of dural integrity. Proper placement of sublaminar wires according to modified Gallie fusion (d).

for *Mycobacterium tuberculosis* complex direct PCR and a Ziehl-Neelsen acid fast smear microscopy, for herpes simplex virus (HSV) 1 + 2 PCR and serology, for fungal microscopy and culture, as well as for CSF immunoglobulin levels. Empiric antibiotic treatment (renal dosing) with vancomycin (1g q12h iv), meropenem (2g q12h iv), and acyclovir (10 mg/kg q12 h iv) was initiated – steroids were tapered and MTX stopped. The patient was admitted with the presumptive diagnosis of meningoencephalitis as surgical site infection (SSI) with secondary hydrocephalus in an immunocompromised host (steroids, MTX). Over the weekend, he suffered of another loss of consciousness (DD: syncope, epileptic) and an EEG showed no epileptiform activity while his overall clinical condition was unchanged since admission. On the following Monday (day 3), magnetic resonance imaging (MRI, Fig. 3) of the brain was obtained and revealed a dilated ventricular system with periventricular edema (Fig. 3a). Synechiae in the frontal horn of the right lateral ventricle (Fig. 3b) and of the left temporal horn (Fig. 3c) as well as moderate contrast enhancement in the infundibular recess of the third ventricle were seen (Fig. 3d). The aquaeduct of Sylvius and foramina Luschkae and Magendii were patent, consistent with communicating hydrocephalus secondary to ventriculitis. Subsequently, a lumbar drain was installed and CSF was drained at a rate of 5 ml/h.

3. Results

Within 2 days the entire symptomatology (headaches, confusion, mnestic deficits, gait disturbance) reversed completely. In the meantime, serology tests (peripheral blood and CSF) as well as blood and CSF cultures came back negative. Acyclovir was stopped (day 6) and meropenem was changed to ceftazidime (day 7, 2g q8h iv) since the cultures did not grow *Listeria* species. Finally, on day 10 the CSF 16S rRNA gene PCR resulted in the identification of *Aggregatibacter aphrophilus* as the causative microorganism. Homology analysis of the 482 bp sequence was performed using Smartgene IDNS^{TM} software (SmartGene, Zug, Switzerland) and showed 100% identity to the 16S rRNA gene of *A. aphrophilus* (100% match with *A. aprophilus* GenBank accession numbers AY362906, EU083529, KC866146, KC866272). The second homologous species was *Pasteurella mairii* with only a sequence homology identity of 93.6% (31 mismatches in 482 bp), allowing the solid assignment of *A. aphrophilus*. Consequently, the antibiotic regimen

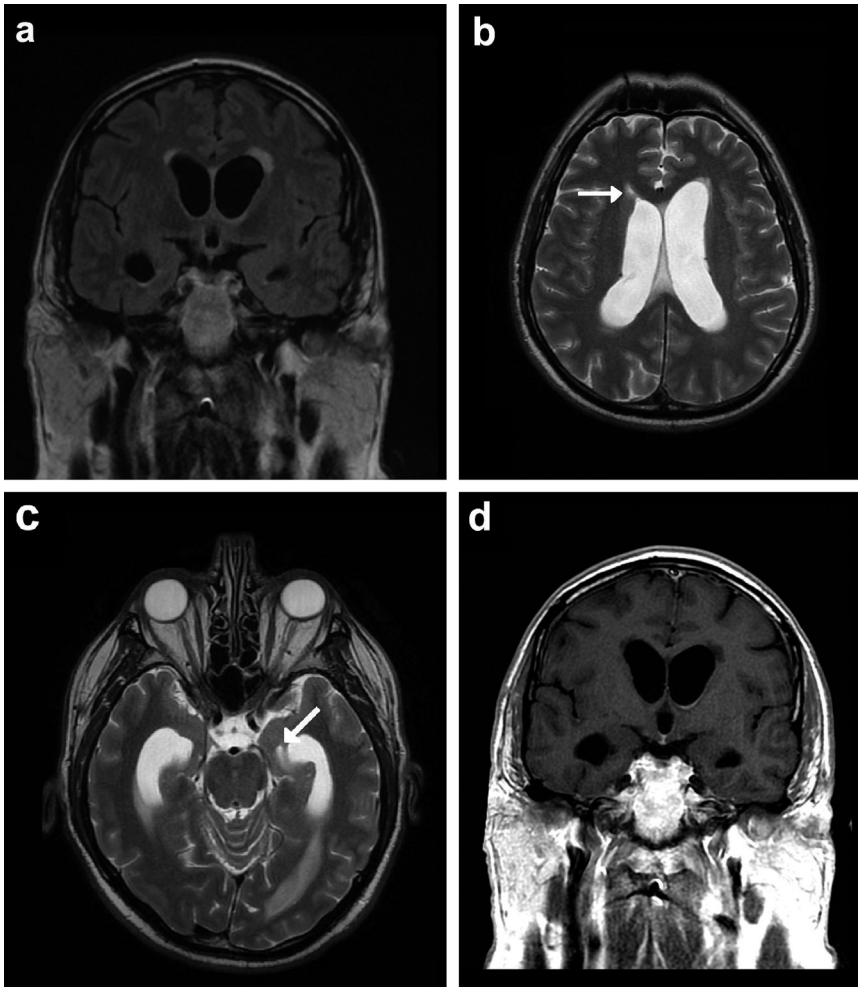

Fig. 3 – Magnetic resonance imaging (MRI) of the brain on day 3 after admission. The dilated ventricular system with periventricular edema can be best appreciated on coronal FLAIR images (a). Synechiae in the frontal horn of the right lateral ventricle and of the left temporal horn can be seen on axial T2-weighted images (b and c). Moderate contrast enhancement (gadolinium) was found in the infundibular recess of the third ventricle as well as lining of the ventricles (d).

was changed to a single regimen of ceftriaxone (2g q12h iv). During the hospital course, the initial leukocytosis came back to normal, the patient was never febrile and never had elevated CRP-levels. Clinical signs and symptoms typically seen in IE could not be confirmed in our patient at any time. Two follow-up cranial CT scans showed stable ventricular size without signs of decompensation. On day 14, the lumbar drain could be successfully weaned without subsequent neurological deterioration, antibiotics were stopped after a total of 14 days of treatment and the patient was subsequently discharged. He moved back to Germany and according to his general care practitioner, he was clinically asymptomatic and had laboratory results within normal limits at 3-months and 6-months follow-up.

4. Discussion

Aggregatibacter aphrophilus (or formerly *Haemophilus aphrophilus*) belongs to the HACEK group of bacteria. The acronym HACEK stands for *Haemophilus* species (i.e. *Haemophilus parainfluenzae*, *H. aphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eiknella corrodens* and *Kingella kingae*. This group of bacteria causes 3 to 10% of native valve endocarditis cases in adults [10] and is the most common cause of pediatric Gram-negative endocarditis [11]. They are traditionally grouped together because all of them are slow growing, requiring special media conditions and all belong to the Gram-negative oropharyngeal flora. In the past, the HACEK group was considered the main causative agents in culture-negative endocarditis, but following improvements in culturing techniques HACEK bacteria can be isolated if incubated for at least five days under optimal growth conditions [12,13]. In this case, blood cultures and CSF cultures were obtained before the initiation of antimicrobial therapy, but remained negative despite prolonged incubation. However, broad range 16S rRNA gene PCR followed by sequencing solidly diagnosed *Aggregatibacter aphrophilus* as the causative agent. For most clinical bacterial isolates partial sequences already provide adequate differentiation for identification [14–16]. A recent review about

molecular diagnostics in brain abscess has shown the clinical impact and the importance of PCR technology as an alternative to culture-based methods in the detection of fastidious bacteria [17]. Another powerful tool to identify rare bacterial diseases is Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (MS), but generally requires a culture isolate for analysis [18]. Our laboratory examined blood and CSF material by standard microbiological culture methods, including blood cultures, culturing in liquid medium (thioglycolate broth) and culturing on solid media (sheep blood-, chocolate- and Brucella agar).

According to the Centers for Disease Control and Prevention (CDC) the reported case would classify as SSI-MEN (meningitis or ventriculitis) as implants were left in place and the infection occurred six weeks after surgery [19]. Clinically significant complications of screw insertion into the cervical pedicle are generally low [20]. Usual intra- and perioperative complications occurring with C1/C2 screw fixation include injury of the vertebral artery (around 2%) [21,22], dural tear with potentially consequent CSF fistula and CSF collection, spinal cord injury, injury of the hypoglossal nerve or the hypopharynx among others. Incidental durotomy ('dural tear') is a potential complication of spine surgery. A recent study has shown a notable difference between cervical (1.3%) and thoracolumbar (5.1%) cases of dural tears [23]. A significant but rare secondary effect of a dural tear caused by a pedicle screw may be an infection of CSF. However, postoperative ventriculitis after spine fusion has not been reported yet.

The most common microorganism of spinal infections is *Staphylococcus aureus* [24] usually causing local wound infections or spondylodiscitis, epidural or subdural empyema and in very rare cases intramedullary abscess. *Aggregatibacter aphrophilus* is not typically found in immunocompromised patients; to our knowledge this pathogen was mostly found in immunocompetent patients [25,26].

On imaging, ventriculitis may not appear in early stages [27]. Recent studies have shown that MRI has been a sensitive technique in evaluation of patients suspected of having meningitis or ventriculitis [27]. On MRI, our patient had typical findings of ventriculitis which include thick ependyma with notable enhancement and dilated ventricles [4].

In retrospect, the aberrant course of the left C1/C2 screw during cervical instrumentation has created a nutrient solution for bacterial infection. Usually, dural tears through C1/C2 fusion techniques occur during the actual passage of the sublaminar wires through the spinal canal for the Gallie fusion (Fig. 2d) [28]. A following *Aggregatibacter aphrophilus* infection of the CSF resulted in ventriculitis (per continuitatem) and communicating hydrocephalus. The bacterium may have been introduced with the screw, however, a contamination of a CSF leak with oropharyngeal flora of the patient seems a more likely explanation. We presume that the infection was facilitated by the iatrogenic immunosuppression as a treatment for the patient's rheumatoid arthritis.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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