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Persistent dysexecutive syndrome after pneumococcal meningitis complicated by recurrent ischemic strokes: a case report

Long-term severe cognitive impairment following pneumococcal meningitis

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Abstract

BACKGROUND

Meningitis is a possible complication of pneumococcal infection concerning acute otitis media and sinusitis. It might compromise cognitive function, both for the infection itself and the vascular events that sometimes follow the acute phase.

CASE SUMMARY

Here we describe the case of a 32-year-old female patient admitted to the emergency room due to extensive pneumococcal meningitis, with a sinus outbreak complicated by candidemia. She presented with extensive laminar ischemic damage in the acute phase, resulting in severe cognitive and behavioral impairment. Four years of follow-up, through neuropsychological assessments and neuroradiological investigations, demonstrated the presence of subsequent vascular events, 3 mo and 2 years after the onset.

CONCLUSION

The case is discussed in light of scientific knowledge of the long-term outcomes of this pathology in order to potentially improve diagnosis and promote better outcomes.

Key Words: pneumococcal meningitis; case report; stroke; cognitive and behavioral functioning; long-term outcome.

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Core Tip: Meningitis is a possible complication of pneumococcal infection concerning acute otitis media and sinusitis. ⁶ We describe the case of a 32-year-old female patient with extensive pneumococcal meningitis, with a sinus outbreak complicated by candidemia. She presented with extensive laminar ischemic damage in the acute phase, resulting in severe cognitive and behavioral impairment. Four years of follow-up, through neuropsychological assessments and neuroradiological investigations, demonstrated the presence of subsequent vascular events, 3 mo and 2 years after the onset. The global functional outcome was unfavorable.

INTRODUCTION

According to the National Health Surveillance Institute, the incidence of acute community bacterial meningitis (BM) was, in 2006, 23 per 100,000 inhabitants, adding together all ages and all bacteria.

In adults over the age of 24, the bacteria involved are: pneumococcus, meningococcus, and, more rarely, *Listeria monocytogenes*, *Haemophilus influenzae* and group B streptococcus^[1].

In developing countries, the annual incidence of pneumococcal meningitis ranges from 1-2 to 20/100,000.

Sites of infection may concern acute otitis media, mastoiditis, sinusitis, pneumonia, and endocarditis. Clinical manifestations include sudden high fever, headache, nausea, vomiting, confusion, drowsiness, convulsion, and in more severe cases, loss of consciousness. Mortality is about 20%.

Long-term studies on survivors have demonstrated that ¹adults after pneumococcal meningitis are at high risk of neurologic and neuropsychologic deficits impairing daily life activities and quality of life. In the Kloek *et al* study^[2], a cohort of 79 patients was evaluated 1 to 5 years after acute illness. After a median of 2 years, 34% of the sample ¹had persistent neurologic sequelae, most commonly hearing loss (27%). On overall neuropsychologic evaluation, patients performed worse than the controls. Primary cognitive deficit as cognitive slowness, associated with longer reaction times, were described^[3,4]. In addition, alterations in executive function have also been reported, with prevalent working memory deficits, difficulty in inhibitory control of automatic responses, visuospatial reasoning, non-verbal learning and verbal abstraction^[3-6]. The alternating subcomponent of attention may also be compromised, together with impairments in the visual-constructive domain and in the mnemonic visuospatial domain^[3,4,6].

Neurological complications are frequent after ³pneumococcal meningitis^[7]. Arterial stroke occurs up to 30% of patients, cerebral venous thrombosis up to 9%, and intracerebral hemorrhage up to 9%^[8]. In the study by Schmidt *et al*^[5], brain swelling was observed in 24% of patients, small vessel vasculitis in 8.5%, impairment of CSF circulation in 7%, and sinus thrombosis in 3%.

Cerebral infarction typically develops within the first few days of the disease when the central nervous system inflammation is most severe. Indeed, meningeal inflammation can lead to profound vascular alterations on the meningeal vessels, creating a vasculitis that participates in cerebral anoxia and alterations in blood flow. Delayed cerebral vasculopathy is a rare, but possible complication^[9].

We hereby report a case of a young woman affected by severe and persistent cognitive sequelae after pneumococcal meningitis due to extensive sinusitis complicated by

candidemia, who presented repeated ischemic damages. We describe the clinical history, the cognitive-behavioral profile, and the functional outcome, during the four years following onset.

CASE PRESENTATION

Imaging examinations

-

Laboratory examinations

-

Physical examination

-

Personal and family history

-

History of past illness

-

History of present illness

-

Chief complaints

A 32-year-old right-handed female educated to 16-years of age, artisan by profession, completely independent in everyday activities and without a history of previous neurological disorders, was admitted to the emergency room due to extensive pneumococcal meningitis, with sinus outbreak complicated by candidemia of pulmonary origin, arising with hyperpyrexia, headache, and neck pain. The patient was pregnant at 39 + 1 wk of gestation and underwent emergency cesarean delivery.

Due to severe neurological instability, a brain MRI was performed revealing bilaterally T2 hyperintensity of the cortex signal in large brain areas. The fronto-polar, insular, fronto-medial and cingulate bilateral regions were affected, with a prevalence of damage on the right side. On this side, the frontal operculum and the inferior lobule, and, to a lesser extent, the superior parietal one, were more clearly involved. The neuroimaging was compatible with extensive laminar ischemic damage in the aforementioned areas. The patient underwent hematological tests to assess thrombotic risk and was assessed with CT-angiography of the cerebral circulation to exclude potential atheromatous plaques. In order to exclude potential artery/venous shunts, a transcranial doppler with bubble test was conducted. The results showed the absence of potential causes for stroke. Additional hematologic exams to exclude autoimmunity pathologies were conducted and were negative. The cerebral fluid exam excluded new bacterial infections.

The patient underwent pharmacological treatment with antibiotic and cortisone. One month after onset, the patient was transferred to a neurorehabilitation center for motor and cognitive rehabilitation. The results of the assessments carried out both during the period of hospitalization and after discharge, are described below. Written informed consent was obtained from the patient for publication of this case report.

Figure 1 shows the timeline of the main stages of the rehabilitative trainings, the different neurological and neuropsychological assessments and neuroradiological examinations, conducted over the range of 4 years.

Figure 1 near here

Table 1 shows the results of each neuropsychological test performed. Some tests were found to be not executable, due to the lack of attention skills.

Table 1 near here

Upon admission to a rehabilitation ward, approximately one month after the event, the neurological examination (T0) showed the presence of isochoric, isocyclic pupils, reactive to direct and consensual light stimulus as well as present GAGs reflex, trigeminal reflexes, cough, and vomiting. The patient showed symmetrical ROTs, CPR

in bilateral flexion, non-elicitable Hoffmann, and bilaterally mentioned prehension reflex. The motor skills were preserved, with the execution of even complex activities, but automatic and aimless movements. The patient was not self-sufficient and required total assistance in most daily activities (Functional Independence Measure^[10], FIM Total: 25, Motor FIM: 18, Cognitive FIM: 7).

She showed herself to be alert, but high distractibility was present as irrelevant stimuli caught her attention. She visually engaged the examiner in all spatial positions and showed occasional imitative responses towards significant others in a framework of inertia, apathy, and the absence of motor and verbal initiative. Due to insufficient attentional resources, the neuropsychological evaluation was not yet administrable in this initial phase.

Three months after the onset and during the rehabilitation process, due to the sudden worsening of neurological conditions, the patient underwent a new MRI which showed the known hyperintensity of the signal in FLAIR at the level of the cortex bilaterally. In particular, the temporal-mesial, insular, frontal-opercular and frontal areas were affected, with slight right prevalence present. A new moderate cortical hyperintensity was found at the level of the right pre and post-rolandic cortex area and in the region of the ipsilateral angular gyrus. RMI also showed a net enlargement of the ventricular system, specifically the frontal and temporal horns, and of the periencephalic liquor sulci. In particular, the Sylvian fissures were enlarged bilaterally, due to pronounced atrophic outcomes (MTA score 3-4). Additionally, the corpus callosum was thinned.

Due to a significant behavioral change, a neuropsychological assessment was performed (T1). The profile was characterized by decontrolled behavior, with distractibility, inability to inhibit irrelevant stimuli concerning environmental demands, disinhibition, hyperactivity leading to impulsive agitation, and automatic utilization behaviors. In addition, we observed temporal, spatial, and personal disorientation. Anosognosia was also observed. Communicative abilities began to convey essential needs, interspersed with automatic perseverative expressions, such as "Can we go outside?", "Is my husband there?", "Can you give me some food?". Neuropsychological

tests showed a severe dysexecutive syndrome with difficulty in controlling automatic responses and marked disturbance of attentional function, particularly for the selective and alternating subcomponents. The sustained attention was partially preserved. In the praxis-constructive domain, the performance qualified as pathological due to difficulties in the executive planning of the realization of the graphic elements.

Six months after the onset (T2), spatial and personal orientation was recovered. The awareness was classifiable in the cognitive level of Crosson's model^[11]: the patient verbally reported the neurological event that occurred as a result of the continuous exposure to that information during the rehabilitation training. On a structured assessment, improvements in selective attention skills were observed, however, attention-shifting skills were still deficient. The dysexecutive syndrome, both for cognitive and behavioral aspects, remained severe. In addition, alterations in social conduct, invasive behaviors, hyperorality, and a tendency to dromomania were present. In the memory domain, the patient presented a main working memory deficit which, with reduction in attention control skills, limited storage and recall processes, mainly for verbal material. The dysexecutive profile affected the correct execution of the tests, leading to fluctuating performance.

Seven months after the onset, the patient was discharged for rehabilitation at the residence area. Upon returning home, the patient was able to carry out the activities of daily life only with the need of supervision or adaptations (Total FIM: 98, motor FIM: 79, cognitive FIM: 19). From the motor point of view, she had regained adequate movement strength. Daily life management was significantly affected by the stability of the behavioral profile, which considerably compromised affective and social relationships.

The neuropsychological evaluation performed at the follow-up 9 mo after the neurological event (T3), showed an increase in accuracy, selection of attentional target, and attentional shifting skills. However, there was a regression of awareness aspects leading to anosognosia. The dysexecutive aspects and the memory difficulties previously noted were substantially stable. However, the loss of inhibitory control

began to affect the sexual sphere as well, with significant behavioral management difficulties. In the praxis-constructive domain, although a greater number of elements have been copied, a pathological performance persisted due to difficulties in the executive planning of the realization of the graphic elements.

At that time, the patient followed attending the recreational center, for people with disabilities where she undertook cognitive stimulation training, with ecological objectives aimed at recovering autonomy. With respect to her functional profile, she never went back to work and the parental role was delegated to her husband.

Two years and five months from onset, the patient suffered a new ischemic event in the pontine region. The RMI showed a small area of altered median-paramedian right signal in correspondence with the floor of the fourth ventricle, hyperintensity in the FLAIR, and long TR images, characterized by signs of restrictive edema in DWI and by nuanced impregnation after administration of contrast medium. The result was compatible with a recent pontine ischemic lesion. **Apart from this new lesion, the remaining findings were compatible with the expected evolution of the previous brain damage.**

At that time the patient started an antithrombotic therapy.

Four years and two months after the onset, the patient underwent a new neuropsychological assessment (T4), which showed a substantially stable cognitive profile compared to the previous evaluation which was characterized by multi-domain difficulties. In particular, deficits in the attention-executive domain were more evident (distractibility due to interference from irrelevant stimuli, slowdown in information processing, deficit of attentional switching capacity, sensitivity to interference and loss of inhibitory control and of cognitive flexibility). Regarding the memory system, scores at the lower limit of the norm were observed in both auditory-verbal and spatial short-term memory tests, as well as deficits in auditory-verbal and visuospatial working memory and in long-term visual-spatial memory. Relative to behavior, compared to the previous evaluation, a slight improvement was observed (a decrease in sexual disinhibition and in use behavior, and the absence of hyperphagia). Instead,

impulsiveness and sometimes inappropriate attitudes to the context remained (timeline of behavioural disturbances are shown in supplementary material). The patient was completely autonomous in carrying out simple daily activities, but needed assistance with regards to more complex activities (Activities of Daily Living^[12]: 6/6; Instrumental Activities of Daily Living^[13]: 2/8). The patient was still anosognosic.

Regarding the rehabilitative interventions, the severity of the cognitive-behavioral framework had not always allowed the setting of structured training. In the initial phase, cognitive rehabilitation sessions focused on attentional exercises aimed at inhibiting the interference of irrelevant information and increasing the ability of sustained attention. Then, with the increasing of attentive skills, the rehabilitation focused on the reorganization of awareness and behavior through cognitive-behavioral methods aimed at reorienting and monitoring impulsivity and verbal perseverations. The patient had also undergone selective and alternating attentional training.

Over time, the objectives have shifted from the restorative plan to the compensatory and functional efficiency plan, up to the inclusion in the recreation center.

MULTIDISCIPLINARY EXPERT CONSULTATION

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FINAL DIAGNOSIS

-

TREATMENT

-

OUTCOME AND FOLLOW-UP

-

DISCUSSION

Here we have described the case of a woman with severe cognitive sequelae, after bacterial meningitis starting from sinusitis and, consistent with the anatomical contiguity, prevalent damage in the frontal lobe, and consequently in executive functions and behavior control.

The patient presented dysexecutive syndrome with a severe behavioral disturbance. The profile has always been highly variable over time whereas it still remains serious. Symptoms are only partially alleviated, and significantly affect the resumption of independent life.

Due to the cognitive and behavioral profile, the clinical observation was more informative than the neuropsychological assessment. Indeed, neuropsychological tests were greatly affected by attention impairment, compromising their administration and reliability. Overall, the patient mostly failed in all attentional and executive function tasks.

With respect to behavioral profile, in the post-acute phase, a Kluver-Bucy Syndrome was even supposed. The syndrome follows bilateral lesions of the limbic system and manifests with personality alterations, bulimia, exhibitionism, compulsive hypersexuality, masturbation, affective indifference, and aggression^[14]. The patient presented with almost all the symptoms, except for aggression.

Compared to behavioral disorders of frontal origin often described in the literature^[15], the patient presented a broad range of symptoms: motivation disorders (reduced purposeful cognition, reduced emotional reactivity, and, in the initial phase, akinetic mutism), disinhibition disorders (motor and cognitive impulsivity, alterations in social conduct such as bizarre attitudes, sexual disinhibition, personhood, hyperactivity, dromomania, environmental dependency), perseverative behavior and anosognosia.

After the severe first neurological damage, the patient had two more strokes in the following months and years which complicated the outcome. **Stroke in young patients may be the manifestation of a specific haematological disease or may appear as a complication in the course of haematological disorders** ^[16].

Nevertheless, thanks to the tests we conducted we tend to exclude this possibility, favoring the hypothesis of complications related to the infection. Indeed, it's known that infections affecting the central nervous system represent a rare cause of cerebral ischaemia. In the retrospective study of Arboix and coworkers ^[17] of the 70 patients with cerebral ischemia from an unusual cause, 11 (15%) presented with central nervous system infections, such as syphilitic meningitis, infective endocarditis, meningococcal meningitis, pneumococcal meningitis, and HIV infection. In our patient, the presence of vascular events repeated over time demonstrates how the suffering of the cerebral vessels on an inflammatory basis can involve a greater risk of occurring in new ischemic events, even at a distance from the acute phase.

The prognosis of our patient appears to have been particularly negative due to the sum of various factors. As already reported in the literature, bacterial meningitis, even when they do not have vascular complications, can lead to long-term alterations in cognitive function^[2-5]. A recent study had hypothesized that macrophage migration inhibitory factor (MIF) upregulation, a proinflammatory cytokine and a neuro-endocrine mediator, contributes to the cognitive impairments of survivors of pneumococcal meningitis^[18]. Several studies showed the association between increased MIF production and Alzheimer disease suggesting MIF involvement in the neuro-inflammatory process occurring in mild cognitive impairment and in cognitive decline^[19].

The case we reported, probably sums up the effects of primary inflammatory damage with those of secondary, repeated, vascular damage. Furthermore, despite undergoing many intensive cognitive rehabilitation training sessions, the improvements obtained over time were reduced. It is likely that the severe deficit of behavioral control has compromised the possibility of benefiting from rehabilitation.

Our case report presents some limitations. The lack of a neuropsychological battery sensitive to the severity of the patient's profile and administered at regular time intervals, may have influenced the case description.

In summary, this case report shows a negative functional outcome in a young patient affected by bacterial meningitis, due to a severe cognitive and behavioral disturbance.

CONCLUSION

Understanding and evaluating cognitive profile in the bacterial meningitis is a critical component of diagnosis and rehabilitative treatment, as it ² can cause severe complications and a poor prognosis for the patient. The description of this case report would highlight some of the clinical and neuropsychological features ² of bacterial meningitis with cerebrovascular complications to improve diagnosis and potentially promote better outcomes.

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| 4 | Adrià Arboix, Carme Jiménez, Joan Massons, Olga Parra, Carles Besses. "Hematological disorders: a commonly unrecognized cause of acute stroke", Expert Review of Hematology, 2016
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| 5 | Taha Ulutan Kars, Zahit Furkan Yorganci, Osman Yaşkıran, Atakan Tekinalp, Sinan Demircioğlu.
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