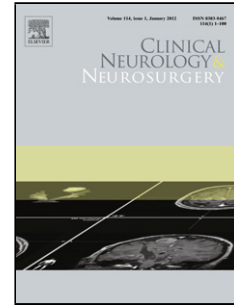


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# FRONTAL LOBE DEMENTIA SYNDROME AS A FIRST MANIFESTATION OF PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM (PACNS)

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**Highlights**

- frontal lobe dysexecutive syndrome as a primary manifestation of PACNS
- widespread cortical atrophy as the only pathological finding on imaging
- indirect histopathological signs of vascular damage give the diagnosis

**Abstract:** This case presents a clinical course of a frontal lobe dysexecutive syndrome with dementia caused by a Primary angiitis of the central nervous system (PACNS) of exclusively very small vessels. Although the clinical manifestations are diverse, an isolated frontal lobe dementia syndrome as a primary manifestation of PACNS has not been reported before. The patient presented with a progressive cognitive decline with loss of memory, disinhibited behavior, parathymic affect and frontal release signs. The diagnostic workup essentially revealed a lymphocytic pleocytosis in the cerebrospinal fluid and a generalized cortical atrophy without any vascular abnormalities. To grasp a diagnosis for this enigmatic clinical picture of a frontal lobe syndrome with signs of inflammation we targeted a tissue-based diagnosis. A brain biopsy gave the decisive hint towards a microvasculitis. Although the histopathologic picture showed peculiarities, a destruction of the vascular bed of very small vessels by lymphocytic infiltration was evident. Our case illustrates an uncommon clinical picture of a PACNS and points to shortcomings of the current histopathologic criteria if only very small vessels are involved.

**Keywords:** Primary angiitis of the central nervous system, cerebral vasculitis, frontal dysexecutive syndrome

## Introduction

Primary angiitis of the central nervous system (PACNS) is characterized by inflammation and destruction of the walls of small- to medium sized parenchymal or leptomeningeal blood vessels. It is a rare disease (2.4/1,000,000 inhabitants) limited to the brain and/or spinal cord that is often lately diagnosed due to nonspecificity of bio- or imaging markers, mostly unknown risk factors, and diverse symptomatology [1].

The diagnostic criteria, formulated by Callabrese and Mallek on the basis of clinical experience, require i) an acquired neurological deficit of unknown origin after a thorough initial basic assessment, ii) a cerebral angiogram with classic features of vasculitis or a biopsy showing vasculitis and iii) no evidence of systemic vasculitis or any other disorder to which such a finding could be secondary [2].

Most patients initially present with chronic and slowly progressive symptoms such as headache, motor weakness, recurrent seizures or aphasia [1, 3] as focal neurologic signs. Although frequently accompanied by cognitive deficits they rarely present the single or initial manifestation of PACNS and are not further described in the literature. This article presents an unusual case of a frontal lobe dysexecutive syndrome with dementia which turned out to be the primary and isolated manifestation of a PACNS.

## Case presentation

A 47-year old, previously well man presented with cognitive deficits progressing for one year. On examination, he showed an atactic gait, a bilateral hand tremor with myoclonus, dysfunctional fine motor skills, symmetric hyperreflexia and a positive glabellar and palmomentar reflex as frontal release signs. Paraphasia and a cerebellar dysarthria marked his speech. In social interaction he displayed inappropriate affect, a foolish attitude, deficits in spatial reasoning, an erratic formal thought and subtle loss of memory. Most impressively was his disinhibited behavior. All of which was preceded by an unintended weight loss of 20 kg.

Initial diagnostic work-up found an increased cell count in the cerebrospinal fluid (CSF) with slightly elevated protein (43 cells/ $\mu$ l, 650 mg/l protein). Cells were predominantly of lymphocytic type and showed no signs of malignancy. Infectious origin was excluded targeting herpes simplex virus, varicella-zoster virus, cytomegalovirus, human immunodeficiency virus, Hepatitis B/C, *Listeria monocytogenes*, *Tropheryma whippeli* and tuberculosis. A neoplastic malignancy was suspected but excluded based on basic laboratory tests, tumor markers, paraneoplastic antibodies (anti-Hu, -Ri, -Yo, -Tr, -Ma, -CV2.1, -Amphiphysin, AMPA, GABA-B, CASPR2, LGI1), abdominal and thoracic CT, colo- and gastroscopy as well as a PET (positron emission tomography)-CT. Tests for oligoclonal bands and proteins indicative of neurodegeneration (protein 14-3-3-, amyloid beta 1-42, 1-40, total CSF tau protein and phospho-tau, neuron specific enolase) were repeatedly negative. Antineuronal antibodies in serum and liquor were repeatedly undetectable.

Interestingly, the first cMRI (1.5 Tesla), about 6-9 months after symptom onset, showed no abnormalities. 6 months later however, for the first time and in subsequent studies, a disproportionate cerebral atrophy was evident (figure 1). Contrast enhanced MR-angiograms (CE-MRA) showed no vascular irregularities. The patient's symptoms of a slowly progressive decline of cognitive functions, mainly manifesting as apraxia and dementia, were accompanied by some episodes of fever and elevated C-reactive protein (CRP).

Ultimately a brain biopsy gave the decisive hint towards the underlying disease: We detected deposition of hemosiderin around small blood vessels using Prussian blue staining and a rarefaction of elastic fibers in the Elastic Van Gieson stain (figure 2). This, together with perivascular accumulation of inflammatory T-cells (CD3, CD8 > CD4), highly suggested the diagnosis of an isolated vasculitis of small cerebral vessels, although the current principal histopathological criteria were not fully met [4, 3]. In the bioptic sample we found intraneuronal A $\beta$  accumulations but no extracellular, especially vascular A $\beta$  deposits.

After the diagnosis was made and almost 2 years after symptom onset, the patient was started on immunosuppressive therapy with an initial bolus of intravenous methylprednisolone (3 days, 1g/d), six monthly administrations of cyclophosphamide at a dose of 750 mg/m<sup>2</sup> BSA and a maintenance therapy of weekly methotrexate 20 mg. This stabilized the course of the disease.

## Discussion

The presented case depicts the diagnostic challenges associated with PACNS due to an uncommon clinical picture: Our patient presented with a relatively fast progressive frontal dysexecutive syndrome as the main manifestation as well as constitutional symptoms preceding cognitive decline. In first line the symptomatology was suggestive for a neurodegenerative course like behavioral variant frontotemporal dementia or, due to the presence of constitutional symptoms, which present only in 8% of PACNS patients [3], a paraneoplastic origin. Finally, the repeatedly elevated cell count in CSF together with abnormalities on cMRI led us to the assumption of an inflammatory origin. Diagnostic criteria rely upon brain biopsy or cerebral angiogram which both have a limited sensitivity and specificity in PACNs. Although the bioptic diagnosis is considered the gold standard, the cerebral angiogram is increasingly conducted. It gives, however, only indirect signs of vasculitic changes like symmetric narrowing of vessels, areas of dilation, beaded-vessel appearance and/or displacement or occlusion of vessels of rather large to medium-sized vessels. These signs can be mimicked by several entities including reversible vasospasms and atherosclerosis, thus having a specificity as low as 30%. The biopsy however has a low sensitivity due to focal and segmental changes and peripheral sampling, it may yield negative results in about 40% of cases. It is often omitted because of its invasiveness. The sensitivity of either approach thus differs in relation to the different vascular beds that are involved (overall sensitivity of biopsy ~62 % vs. angiography 73%, [5]). Our patient showed widespread cortical atrophy whereas the CE-MRA showed no vascular abnormalities. This suggested involvement of small vessel in which the diagnostic yield of biopsy over angiogram is higher due to the peripheral sampling.

In this case, a bioptic diagnosis should be aimed and it should target abnormalities close to the leptomeninges to increase the sensitivity [3].

Of specific interest in the present case is the fact that the biopsy clearly suggested a microvasculitic origin although the current histopathological criteria were not fully met. These require a vasulocentric transmural inflammation marked by lymphocytic infiltration and damage, with or without fibrinoid necrosis. Not mandatory, but often, granuloma formation through the vascular wall is found or extracellular amyloid deposition in the vessel walls. Since secondary involvement of vessels to an encephalitic or infectious process is common, a clear dominance of vascular to parenchymal infiltration is required for differentiation [4]. In our patient, since only very small vessels were involved, a transmural inflammation was not directly traceable. We found however indirect signs, clearly pointing to a destruction of the vascular integrity: leaky vessels, a decay of the vascular wall and perivascular infiltrations of inflammatory T-cells (CD3, CD8 > CD4). The presence of vascular damage in areas of only little parenchymal affection was decisive for the interpretation of a causal influence of vascular destruction to parenchymal loss. In the context of a reduction in working memory capacities in our patient we looked for distinguishing signs to a neurodegenerative process like in Alzheimer's disease. In fact neither extracellular plaque formation nor tau deposition was detected so that we don't attribute a pathophysiological role of this intracellular A $\beta$  to the clinical presentation of our patient.

### **Conclusion**

Taken together a lot can be learnt from our case. In particular the unusual clinical presentation highlights the protean manifestations of PACNS and teaches clinicians to consider PACNS even if acute onset and vascular abnormalities in neuroimaging are lacking. This case calls for an early tissue based diagnosis if involvement of small vessels is highly suspected.

### **Conflicts of interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

### **Ethical standards and Consent**

Written informed consent was obtained from the patients' guardian for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

### **Authors' contributions**

MB: clinical course, writing the manuscript

KO: clinical course

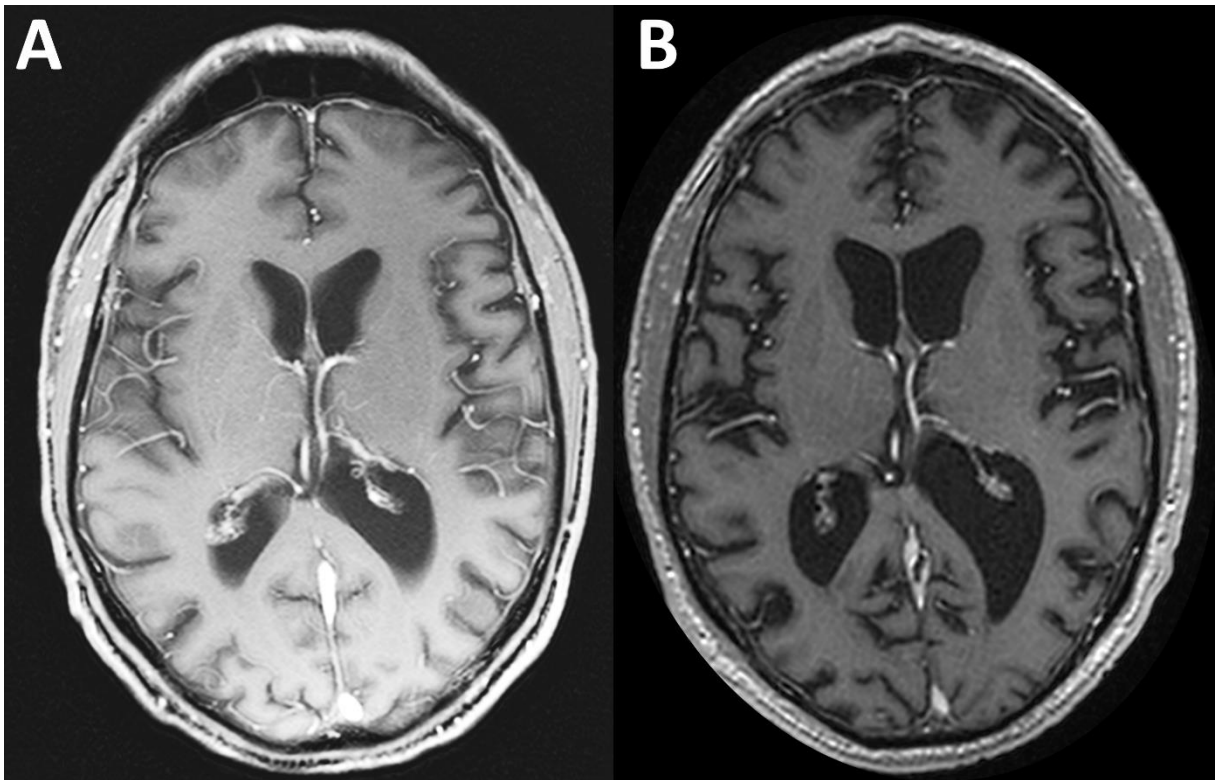
MG: neuropathologic diagnosis

TM: clinical course, writing the manuscript

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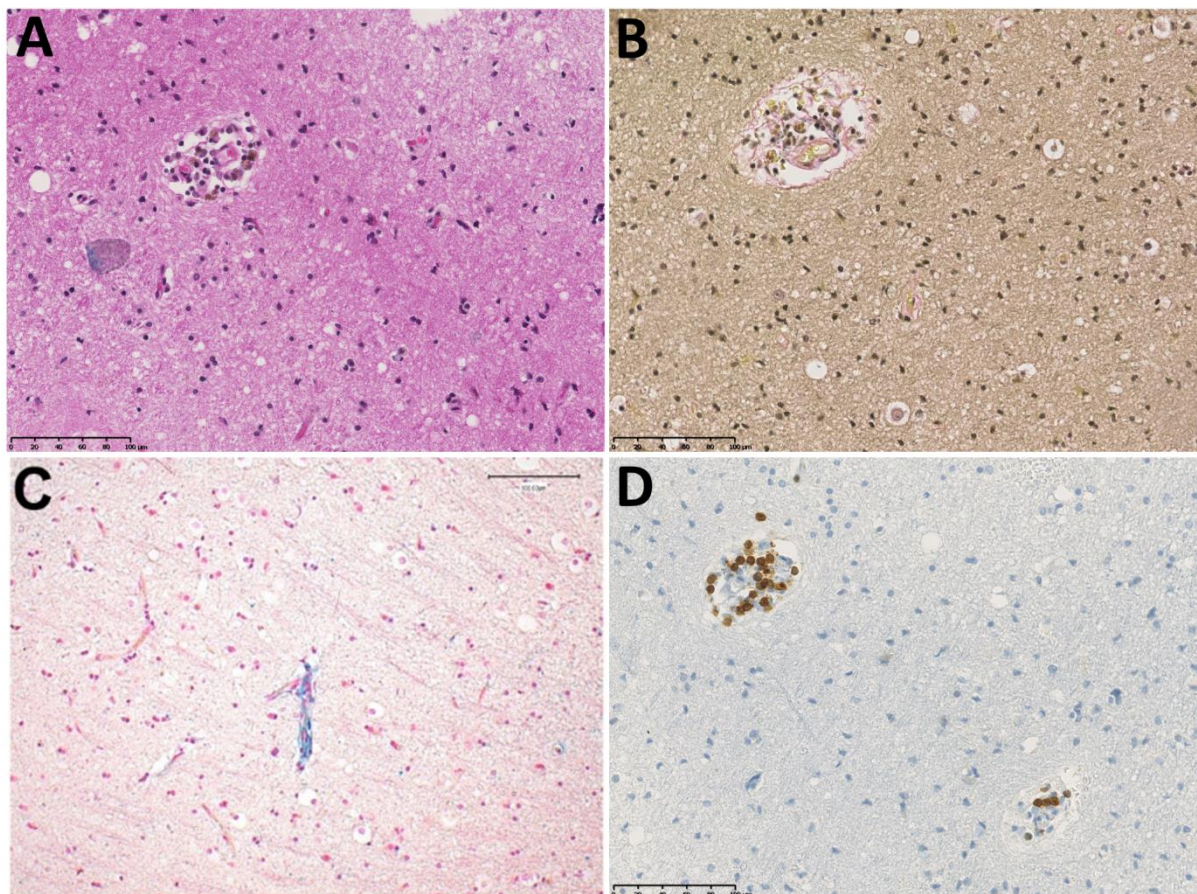
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## Figure legend



**Figure 1** Axial T1 weighted cMRI 9 months after symptom onset (A) compared to 33 months after symptom onset demonstrating widespread, generalized cortical atrophy especially at the insular cortex, opercula with ventricular widening but also detectable at the frontal and parietal lobes.





**Figure 2** Pathologic features of microvasculitis. *Hematoxylin* and *eosin* (A) and Prussian blue (C) staining showing hemosiderin around small blood vessels indicative of leaky vessels. Perivascular and sparsely intramural accumulation of inflammatory T-cells (D, CD3) in the absence of parenchymal inflammation. Rarefaction of elastic fibers in the Elastic Van Gieson stain (B).