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Short Communication

Cryptococcal Meningitis Misdiagnosed as Alzheimer's Disease: Complete Neurological and Cognitive Recovery with Treatment

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Abstract. A sixty-two year old man, with a background of Alzheimer's disease for the past three years, acutely presented with imbalance, headaches, and dizziness. Examination revealed a profound frontal disinhibited and dysexecutive syndrome and brain imaging notable for leptomeningeal enhancement; laboratory data confirmed cryptococcal meningitis. Four months after treatment, the patient was normal neurologically, cognitively and neuroradiologically. The specific cognitive impairment and neuroradiological findings may be clues to differing dementia etiologies.

Keywords: Cryptococcal meningitis, dementia, frontal syndrome

INTRODUCTION

With the increasing number dementia subtypes appreciated, conditions that masquerade as dementia, and the emergence of differing treatment choices, a precise diagnosis is imperative. In an era of limited physician-patient interaction time and the tendency to limit cognitive testing in clinics to the Mini Mental Status Examination (MMSE), conditions such as frontotemporal lobe disorders are simply not diagnosable. Commonly occurring cognitive impairment entities, such cognitive vascular disorders as well as other similarly presenting cognitive syndromes caused by infectious, inflammatory, metabolic, and demyelinating diseases and traumatic brain injury may consequently be confused when patients are paucisymptomatic, especially with equivocal clinical and neuroradiological results. All these conditions are characterized by frontal network disturbances of varying degrees and type, usually impervious to deciphering by the MMSE, which is lacking in frontal systems inquiry.

INDEX PATIENT

A sixty-two year old white male presented with blurry vision, imbalance, headaches, and dizziness to the emergency department and was given a provisional diagnosis of posterior circulation infarct or posterior fossa syndrome. His wife had noted a subtle personality change over the last three years. Both his family and friends had become aware of a lack of tact that was very different to what they were accustomed to. He was described as thoughtful and caring. He had been assessed by a neurologist three years previously and given a diagnosis of Alzheimer's disease after clinical evaluation and an MMSE score of 24/30 as well as magnetic resonance brain imaging (MRI) and cerebrospinal fluid (CSF) analysis (elevated CSF protein, no cells).

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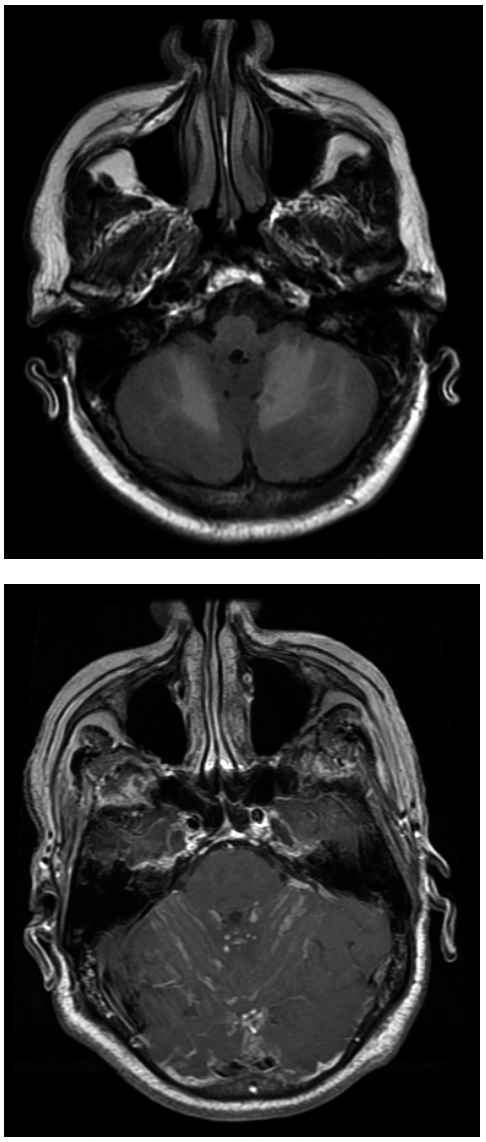
The MRI brain scan had a subtle abnormality at the time of meningeal enhancement. He was treated with donepezil and periodically followed over the three year period. During the last year before presentation to our center, he had deteriorated in that he (verbatim from wife six weeks post event) "cussed frequently, would yell for anyone making a loud noise, would clench teeth and get mad when wasn't what he wanted, he would tell people what he thought of them, was short tempered, would not brush teeth, or take a shower and displayed lack of personal hygiene". He was noted to be very belligerent in the emergency room on his most recent presentation. His only medication was methimazole for hypothyroidism, a drug known to cause leucopenia, albeit rarely.

EXAMINATION

The emergency admission examination revealed an alert, cooperative man with normal vital signs, without stigmata of generalized disease, specifically no bradycardia and no signs of meningism. He was orientated for date, name and place of presentation. Speech was fluent, comprehension normal and he was able to perform five consecutive serial 7's subtractions. Cranial nerve testing was notable for normal pupils, visual fields, no nystagmus but abnormal Rinne and Weber testing implicating a sensorineural hearing loss of the right ear. Sensorimotor testing and coordination testing was normal but a wide-based gait was evident and he was unable to tandem walk and failed the Romberg's test.

SUBSEQUENT LABORATORY DATA

Relevant laboratory data included a normal complete blood count, electrolytes, creatinine of 1.6, VDRL negative, HIV-negative, Lyme antibodies negative, ESR 12, ANA negative, SPEP normal, blood glucose of 116 mg/dl, urine drug screen negative and thyroid function studies normal. The CSF was notable for abnormal opening pressure (recorded as 270 mm water) with glucose 50 mg/dl, protein 137 (normal 12–60 mg/dl), white blood cell count 103, red blood cells 250, lymphocytes 94%, macrophages 5%. India Ink was negative but cryptococcal antigen positive on two subsequent measurements.



(a)

(b)

Fig. 1. The initial MRI demonstrated extensive leptomeningeal nodular enhancement and vasogenic edema. (a) Axial T1W with gadolinium contrast demonstrates extensive nodular leptomeningeal enhancement consistent with exudates due to meningitis. (b) FLAIR imaging demonstrates vasogenic edema and secondary mass effect upon the fourth ventricle. The exudate is T2 hyperintense.

NEURORADIOLOGY

An MRI brain scan revealed posterior leptomeningeal enhancement and bilateral cerebellar hyperintense lesions. Subsequent MRI brain scanning two months later showed marked decrease in T2 signal enhancement and resolution of diffusion abnormalities. These appearances resolved to normality on subsequent scanning four months post treatment.

COGNITIVE METRIC TESTING

Six weeks after his treatment for cryptococcal mengintis with 5 fluocytosine and amphoteracin B, he was evaluated from a cognitive point of view. A battery of frontal network tests and executive function tests were administered. In addition he was evaluated with metric memory tests, language testing, for depression as well as the overall MMSE Score. The Frontal Systems Behavioral Inventory (FRSBE) records three frontal sub-syndromes of apathy, disinhibition and executive function, scored separately by the patient and a family member both for before or during illness and after illness measurement [1]. These T scores were markedly abnormal for self-rated and family rated scales (normal is 50 $+/-$ 10). Disinhibition was the most abnormal, in addition to the apathy and executive function scores during the illness period. Both the family and self reported FRSBE sub-scores were markedly abnormal during the illness and recovered to normality post treatment. The normal scores are represented as T scores with a mean of 50 and a standard deviation of 10 with higher numbers, that is 60 or more indicated significant frontal systems abnormality. The family FRSBE T-scores during illness were apathy (78), disinhibition (101) executive function (79) and total scores were (95). Two months after treatment the scores had all normalized to apathy (51), disinhibition (55) executive function (49) and total score of (51). The FRSBE self reported during illness scores were very comparable with T scores in the same order before illness reading; 82/115/84/100 and after treatment 42/48/48/45. Emotional Intelligence Test (Baron EQ) [2] reported in standard scores (normal is 100 with standard deviations of 10), post treatment evaluation was normal with a total score of 106, intrapersonal EQ subscore of 106, interpersonal EQ score 105, stress management 102, adaptability 113 and general mood score of 96 all within normal range for age, education and gender. The Delis Kaplan Executive Function System (DKEFS) test revealed normal post treatment scores for the Color Word Interference subtest, Tower subtest, and Proverb subtest [3]. Memory as tested with the Repeatable Battery for the Assessment of Neuropyschological Status (RBANS) post treatment revealed standardized scores for (normal is 85-115) Immediate memory 90, visuospatial memory 87, Language 98, attention 91, and delayed memory 102, with an overall score of 90 [4], all within normal range. Language function screening by the Boston Naming Test was 60, which is the maximum score attainable [5]. The MMSE was 30/30 and depression screening by the Centers for Disease Depression Scale Score was 26 reflecting mild depression [6].

DISCUSSION

In this immunocompetent, HIV-negative male, a frontal network syndrome characterized mainly by disinhibtion dominated the presentation. The insidious onset and relatively subtle cognitive disturbances that were sufficiently indistinct from dementia confounded the presentation. Few similar examples have been reported previously but without a comprehensive assessment of the cognitive profile in contradistinction to our patient [7,8]. The complete return to normality as evidenced by his family and our extensive bedside and metric cognitive assessment is particularly noteworthy in someone who would almost certainly have died without appropriate treatment. He clearly did not have Alzheimer's disease to begin with. He represents an example of someone misdiagnosed as Alzheimer's disease because of the complete resolution of all cognitive and neurological deficits with antifungal treatment. Late in the course of his illness, the red flags were clearly the meningeal enhancement and cerebellar lesions. The India Ink test has a sensitivity of only 50–70% and without a confirmatory cryptococcal antigen testing of the CSF a false negative diagnosis of cryptococcal meningitis might easily be entertained.

The cognitive disturbances described with cryptococcal meningitis have mostly taken the form of acute confusional psychosis, mania and encephalopathy state [9–12] in addition to more elementary neurological presentations such as sensorineural hearing loss and headache [13]. He had presented with a florid frontal network syndrome dominated by disinhibition with complete recovery as tested by the FRSBE, corroborated by the normal emotional intelligence scores, and Delis Kaplan Executive Function testing. The presentation could have been better diagnosed as frontotemporal degeneration such as Pick's disease rather than Alzheimer's disease. No features of hypothryroidism were noted either clinically or by laboratory testing discounting this as a possibility of dementia.

Neuroradiological findings in meningitis are best or only demonstrated by MRI with gadolinium contrast with enhancement of exudates in the subarachnoid spaces and leptomeninges. The exudates are T2 hyperintense in FLAIR and T2 weighted images. There may be associated vasogenic edema in the adjacent white matter resulting in mass effect. If the meningitis is untreated, cerebritis and abscess formation can occur. In this patient, the focus of lesion abnormality was entirely within the cerebellum as well as some degree of lep-

tomeningeal enhancement. The latter has also reported previously with cryptococcal meningitis [14–16].

There is a considerable and growing literature of frontal network syndromes in addition to other cognitive syndromes related to isolated cerebellar lesions of various types. We feel that this is the likely mechanism and is postulated to be due to impairment related to the cerebellum which is modulatory for the neural circuits that link it with the prefrontal, posterior parietal, superior temporal and limbic cortices [17–19].

The clue to an earlier diagnosis in this patient was undoubtedly the leptomeningeal enhancement which exists with a number of neurological diseases most particularly chronic meningitides such as cryptococcal meningitis. CSF analysis would have of course have been diagnostic bearing in mind the problem with India ink negativity but with Cryptococcal antigen analysis this is much improved. The 2001 evidence based AAN guidelines on diagnosis of dementia do not recommend routine CSF analysis nor CSF biomarkers [20]. Syndromes that may masquerade as dementia and for which screening is recommended include depression, B12 deficiency, hypothyroidism and syphilis (only if clinically suspect or from endemic regions).

Our case report is not the only patient with cryptococcal meningitis masquerading as Alzheimer's disease [7, 8]. There may be many more unreported ones and because of the insidious nature and covert presentation of chronic meningitis syndromes, ones that remained undetected. Notably there are other chronic infections such as syphilis and connective tissue disorders that can present as dementia yet are curable [21–23]. Although not advocating routine CSF analysis for patients presenting with clinical dementia, we would suggest that the current AAN guidelines be revised to encourage a very low threshold for performing routine CSF analysis in patients presenting with dementia. In addition the more precise profiling of cognitive impairment may yield clues to the appropriate diagnosis.

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