Schizophrenia-like psychosis and aceruloplasminemia

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Abstract: Schizophrenia-like illnesses occur in a variety of medical and neurological conditions but to date have not been described in association with aceruloplasminemia. Aceruloplasminemia is an autosomal recessive disorder of iron metabolism which leads to iron deposition in the basal ganglia, thalamus, cerebellum and hippocampus and which usually presents in middle age with extrapyramidal symptoms and dementia. We describe a 21-year-old woman on treatment for aceruloplasminemia who presented with schizophrenia-like psychosis and declining function in the absence of neurological signs. Neuropsychological testing showed significant dominant hemisphere deficits. Magnetic resonance imaging showed bilateral iron deposition in the cerebellar dentate nuclei and thalami, frontal atrophy, and periventricular white matter hyperintensities. Functional imaging suggested global hypoperfusion. The clinical, cognitive and imaging findings were not typical for either aceruloplasminemia or schizophrenia alone and the possible relationship between the two disorders is discussed with particular reference to implications for our understanding of schizophrenia.

Keywords: aceruloplasminemia, schizophrenia, psychosis

Introduction

Numerous medical conditions are known to produce psychotic symptoms that resemble schizophrenia, including metabolic and neurological disorders (Cummings 1996). We describe a young woman with schizophrenia-like psychotic symptoms and functional decline in the context of diagnosed aceruloplasminemia, a disorder which has not been previously associated with psychosis.

Case history

BB was a 21-year-old woman referred for neuropsychiatric assessment on the background of a psychotic illness and a confirmed diagnosis of aceruloplasminemia. BB's family had noticed an initial 18-month period of functional and social deterioration, poor school performance, social withdrawal, and periods of verbal aggression. She was initially treated by her general practitioner with fluvoxamine, but later deteriorated with frank persecutory delusions, auditory hallucinations, aggression and poor self-care over the subsequent 6 months. The local mental health team began risperidone 3 mg/day, which treated the positive symptoms but did not arrest her functional decline. BB completely avoided all social contact, only watched television and was unable to manage her activities of daily living. She was referred for neuropsychiatric assessment to further elucidate the contribution of the aceruloplasminemia to her cognitive and functional abilities.

BB had no formal psychiatric history. She had mild learning difficulties as a child, but attended mainstream schooling. At age 15 she had seen a school psychologist after telling other students she was going to be reborn as a prince. BB had been diagnosed with aceruloplasminemia at age 20, after detection of abnormal liver function and hyperferritinemia of 1700 μg/L (15–200). Liver biopsy confirmed significant iron

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overload without fibrosis, and desferrioxamine 20 g thrice weekly was initiated. The diagnosis of aceruloplasminemia was highly suspected because a paternal uncle had been diagnosed with the disorder. The patient and her maternal uncle share a common, unique mutation for this disorder. BB's uncle had been described by the family as suffering long-standing behavioral problems but had never been given a psychiatric diagnosis. There was a history of consanguinity, with her parents' grandparents being first cousins.

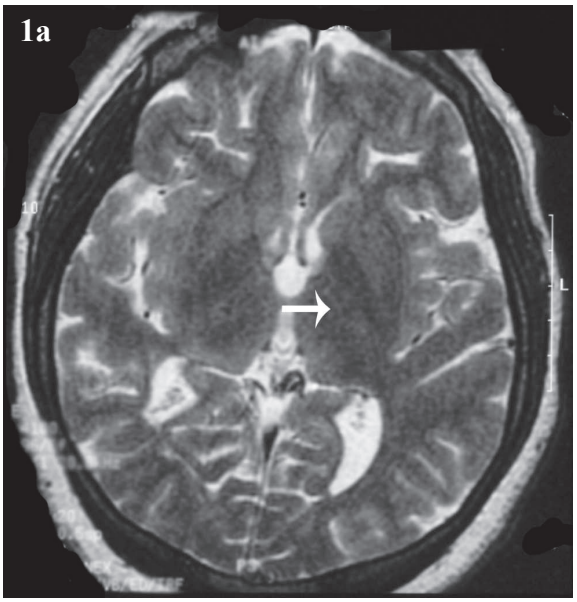
BB's delivery was normal but for a prolonged rupture of membranes. She walked at 12 and talked at 15 months. She was a shy and clingy child at school who had verbal and social difficulties. She left school in Year 11 and attended a technical college where she also struggled. She had not worked or attended school since the age of 18. There was no history of substance abuse.

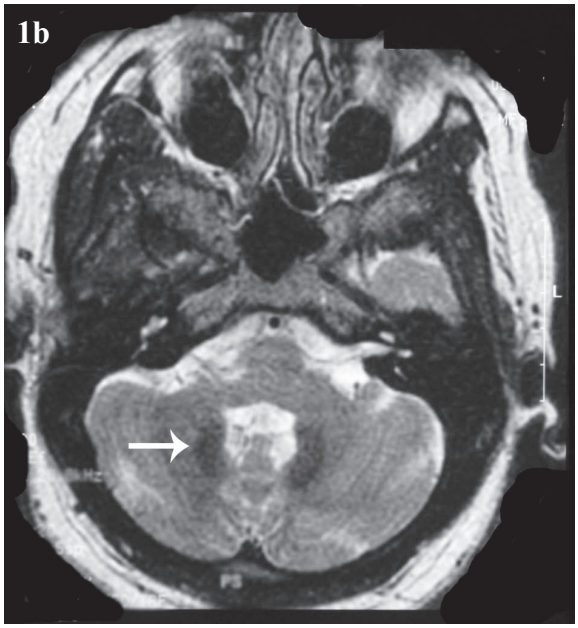
On mental state examination, she was cooperative but only established superficial rapport. Speech was of normal rate and volume with limited spontaneity. Mood was euthymic and affect reactive, although blunted. At the time of assessment there were no psychotic or depressive symptoms and no insight into her previous symptoms or functional impairment.

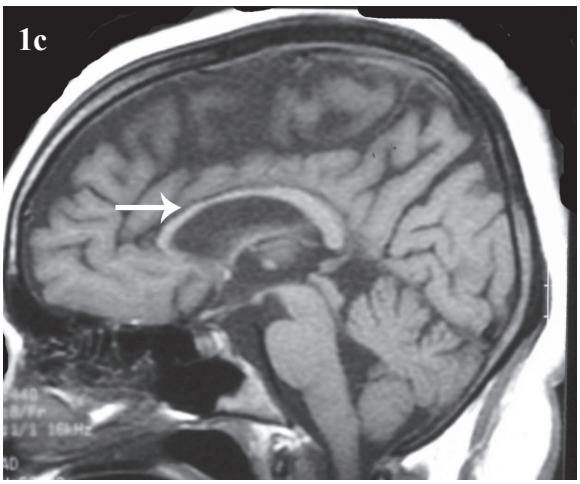
On bedside cognitive testing, she scored 25/30 on the Mini-Mental State Examination (Folstein et al 1975), and 75/100 on the Neuropsychiatry Unit Cognitive screening tool (NUCOG) (Walterfang et al 2006), each significantly below expected age norms. Hence, the patient was referred for a neuropsychological review, and information from an earlier assessment was obtained as a baseline. Physical examination was unremarkable. She had some mild conjunctival pallor but no Kaiser-Fleischer rings. She had no abdominal organomegaly. There were no abnormal movements, primitive reflexes or other neurological signs.

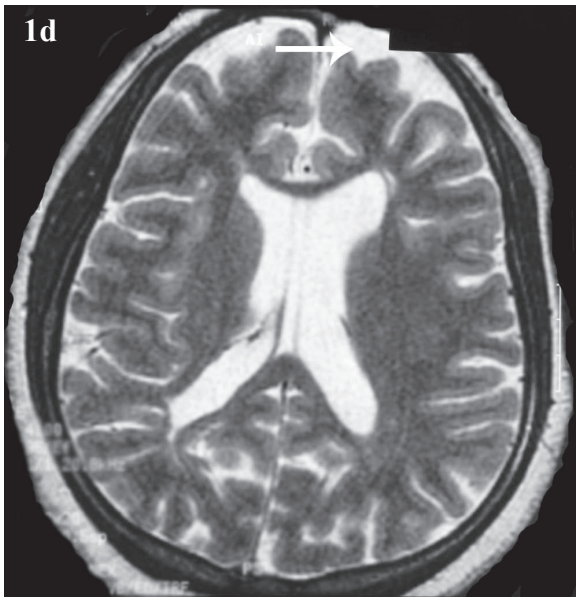
BB had normal electrolytes, hepatic, renal and thyroid function. Hemoglobin was low at 101 g/L (115–150) with normal platelet and white cell counts and B12 and folate levels. Serum ferritin was still elevated at 688 µg/L (15–200).

Magnetic resonance imaging (MRI) showed global atrophy, most marked over the frontal lobes. She had a greater-than-expected load of periventricular white matter hyperintensities, and a thin anterior callosum. Iron deposition was evident in the dentate nucleus of the cerebellum and the thalamus, and to a lesser degree throughout the whole cerebral cortex, but not in the basal ganglia (Figure 1). Single-photon emission computed tomography (SPECT) showed









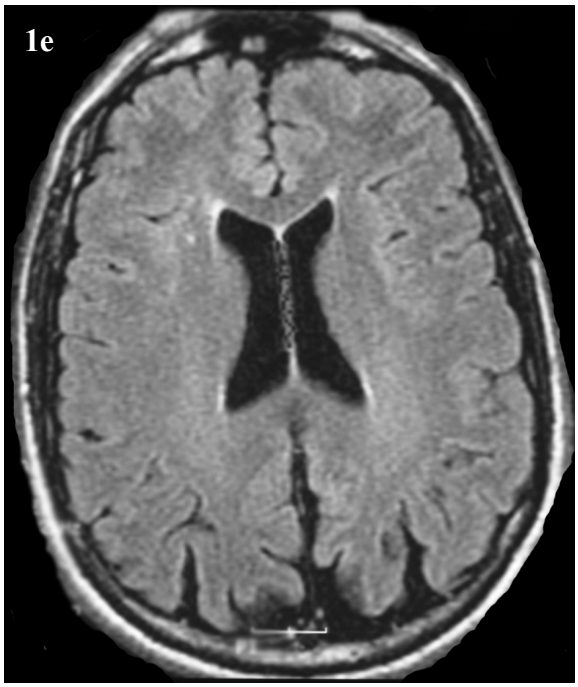


Figure 1 MRI images (with annotating arrows) demonstrating low signal on T2-weighted axial imaging representing iron deposition in the basal ganglia (1a) and dentate nucleus of the cerebellum (1b). Sagittal T1-weighted image demonstrates anterior callosal thinning (1c), likely secondary to frontal cortical atrophy as seen on a T2-weighted axial slice (1d). Fluid-attenuation inversion recovery (FLAIR) axial slice shows periventricular "cupping" (1e).

global hypoperfusion. MRI of the abdomen showed no evidence of ovarian iron deposition. EEG was normal. A screen for lysosomal and other storage disorders on peripheral blood lymphocytes and cultured fibroblasts was normal.

Neuropsychological assessment showed a woman of low-average to average premorbid intellect, but demonstrating borderline general intellectual ability suggesting a significant decline. She performed significantly better on non-verbal than verbal tasks, which were poor, in addition to poor verbal memory. Working memory was very poor, and psychomotor speed and speed of information processing was slowed. She had strengths in visuospatial/constuctional abilities and memory. She displayed good performances on frontal-based tasks tapping into generating new strategies, response monitoring, inhibition, planning and organization, and mental set-shifting, although she was at times significantly slower than her age-peers. These deficits were also borne out in an occupational therapy assessment, where her deficits of new learning were manifest in requiring frequent repetition to learn new tasks, and slow mental information processing impaired her ability to deal with everyday financial and logistical tasks.

The patient's risperidone was increased to 5 mg per day, with some improvement in her degree of negative symptoms without re-emergence of positive symptoms. Eighteen months after assessment, she had begun a beauty therapy course.

Discussion

Ceruloplasmin (CP) is a 132-kDa glycoprotein that is predominantly synthesized in the liver but does not cross the blood brain barrier and is produced by astrocytes in the CNS (Klomp and Gitlin 1996). Copper atoms incorporated during the synthesis of CP allow it to shuttle electrons and act as a multicopper ferro-oxidase. In iron homeostasis CP oxidises Fe^{2+} (ferrous iron) to Fe^{3+} (ferric iron) so that the latter can bind to transferrin and be trafficked throughout the body. Fe^{2+} is required as a cofactor for many biological processes but is capable of generating toxic hydroxyl and superoxide free radicals, and hence must be tightly bound to proteins during transport and storage (De Silva et al 1996). CP promotes the loading of iron onto transferrin, allowing Fe^{3+} efflux out of cells and preventing oxidative damage caused by Fe^{2+} (Qian and Ke 2001; Hellman and Gitlin 2002).

In aceruloplasminemia, an autosomal recessive disorder occurring in 1 in 2 million non-consanguinous births (Miyajima et al 1999), mutations in the CP gene result in absent ferroxidase activity of CP leading to the deposition of iron in the CNS, retina, pancreatic cells, liver, spleen, and ovaries (Yoshida et al 1995; Hellman and Gitlin 2002). The astrocyte-specific form of CP plays a key role in regulating iron levels in the CNS and in preventing free radical injury (Patel et al 2002). The major sites of CNS iron deposition in

aceruloplasminemia are the basal ganglia, cerebellar dentate nuclei, red nucleus, thalamus, and hippocampus (Miyajima 2003). The pattern of deposition, which is greatest in the globus pallidus and putamen (Miyajima 2003), occurs in regions where vulnerable perivascular astrocyte populations are distributed (Klomp and Gitlin 1996). The sites of greatest iron concentration in healthy individuals are the basal ganglia, red nucleus, and deep nuclei of the cerebellum (Yoshida et al. 1995).

Aceruloplasminemia presents with retinal degeneration, diabetes mellitus and neurological symptoms, usually extrapyramidal signs, dyskinesia, dystonia, and a subcortical dementia in the fifth or sixth decade (Nittis and Gitlin 2002). Neurological signs may be preceded for many years by diabetes mellitus and anemia due to inefficient iron delivery. MRI findings typically show marked T2 hypointensity in these regions of maximal iron deposition(Morita et al. 1995; Daimon et al. 1999; Grisoli et al. 2005), although may also show subtle posterior white matter tract hyperintensity and subtle superficial cerebral and cerebellar cortical hypointensity (Grisoli et al 2005). White matter tract changes may reflect a disconnection of projecting fibres from key relay nuclei such as the thalamic nuclei, with subsequent subtle cortical changes (Grisoli et al 2005).

While the clinical presentation was predominantly one of schizophrenia with no classical neurological features of aceruloplasminemia, the imaging findings of thalamic and cerebellar involvement suggest that even at this early stage CNS manifestations of aceruloplasminemia are present but neurologically silent. BB's imaging also revealed prominent frontal cortical atrophy, white matter hyperintensities and thinning of the corpus callosum which are not characteristic of CP (Miyajima 2003) and no other pathological cause was found for these changes. Regional cortical and callosal atrophy of this nature, as opposed to subtle cortical and white matter intensity changes, have not previously been reported in aceruloplasminemia.

The MRI findings of significant iron deposition in the thalamus and the dentate nucleus of cerebellum may be relevant to her schizophrenia-like presentation. The repeated demonstration of subtle abnormalities in structure and function of the cerebellum in schizophrenia populations has also led to its implication in the development of schizophrenia, possibly due to disruptions to the cerebello-thalamo-cortico-cerebellar loop (Andreasen et al 1998). Pathology in the thalamus may also disrupt this circuit, and given that the thalamus has similarly been implicated in the pathogenesis of schizophrenia (Clinton and Meador-Woodruff 2004), it is feasible that iron deposition-related pathology in these regions may be, in a vulnerable brain, psychotogenic.

The development of psychosis in BB, atypical for aceruloplasminemia, could be seen to represent an " organic'' example of the " two-hit" model of schizophrenia. The effects of aceruloplasminemia through pathology in dentate and thalamic regions in BB may have interacted with an early frontal insult, such as perinatal hypoxia or other obstetric complications – known risk factors for the later development of schizophrenia (Cannon et al 2002a, 2002b) – or with other unknown biological vulnerabilities, to result in schizophrenia-like symptoms during the typical age of onset for the disorder. There is a strong relationship between anatomic abnormalities in the hippocampus, cerebellum and thalamus and schizophrenia (Harrison 1999; Shenton et al 2001) and iron deposition in these regions during adolescence may have triggered a vulnerability to schizophrenia-like psychosis in this patient.

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