Alice in Wonderland Syndrome as a Manifestation of Creutzfeldt-Jakob Disease

Sir,

Alice in Wonderland syndrome (AIWS) is a perceptual disorder that involves distortions of visual perceptions, the body schema, and the experience of time.[1] Despite being assumed as a rare syndrome, large-scale population studies have revealed a lifetime prevalence of up to 30% in the general population of experiencing a transient symptom involving a single phenomenon (mostly micropsia or macrosomatognosia).[2,3] In a cross-sectional study of 297 healthy individuals with a median age of 25.7 years, a prevalence rates of 30.3% for teleopsia, 18.5% for dysmorphopsia, 15.1% for macropsia, and 14.1% for micropsia were observed.[4] This study also showed that 38.9% of the affected individuals experienced a single symptom, 33.6% experienced 2, 10.6% experienced 3, and 16.8% experienced 4 symptoms. In the largest systematic review by Blom *et al*,[5] AIWS was reported in total 166 patients in literature. The common diseases being migraine, Epstein–Barr viral infection of brain, drugs, epilepsy, head injury, etc. Although the majority of cases are fleeting and non-persistent in nature, some can be serious and even lethal in conditions. Although majority of the cases are self-limiting, others may require neurological or psychiatric consultation, and yet, it is not a well explored entity in either of the specialty. This may be partly due to limited attention and description in major disease classifications such as the ICD-10 and the DSM-5 and probably also due to relatively small number of published cases.

Herein, we report a case of AIWS in a patient with AIWS who was diagnosed with Creutzfeldt-Jakob disease. The aim of this report is to increase awareness and understanding of AIWS among clinicians and to highlight the importance of considering its potential association with severe and even lethal conditions.

Case Report

A 61-year-old male presented with sudden onset blurring of vision. Ophthalmological evaluation revealed left-side hemianopia with normal fundus and color vision. Over the next few days, the patient complained of objects shrinking or swelling up to an abnormal size (micropsia and macropsia), speeding up of moving objects to his face, and hyperchromatopsia. He also reported that straight lines appeared wavy, and he had difficulty appreciating depth while walking. After 2 weeks, he developed imbalance during walking and short-term memory loss.

Neurological examination revealed recent memory impairment, impaired complex arithmetic calculation, and impaired categorical and word fluency. The patient was unable to do tandem gait and had stereotypical abnormal movements of the right upper limbs in the form of repetitive combing movement. His complete hemogram and metabolic profile including thyroid function and ammonia levels were normal. Vasculitis profile including anti-thyroid peroxidase antibody and anti-thyroglobulin antibody were negative. Cerebrospinal fluid (CSF) analysis revealed colorless fluid with normal cells, protein, and sugar levels, and negative virology panel and for malignant cells. CSF autoimmune encephalitis profile was negative with negative serum paraneoplastic profile. 14-3-3 protein quantification in CSF was positive (75964 AU/ml).

Magnetic resonance imaging (MRI) of the brain showed DWI restriction along fronto-parieto-occipital cortex, characteristic of cortical ribboning, and electroencephalogram demonstrated sharp wave discharges at irregular intervals with background slowing [Figure 1a and b] Computed tomography (CT) scan of thorax and abdomen was done and were normal. A probable diagnosis of sporadic CJD was made.

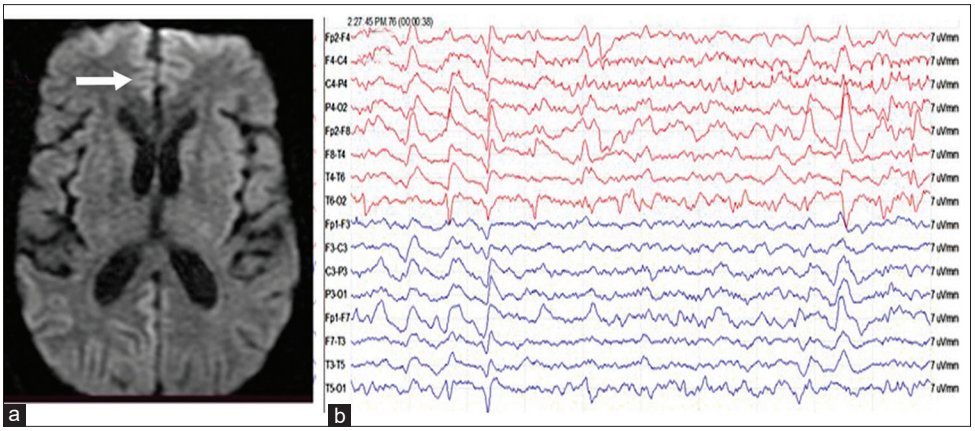

Figure 1: Axial DWI section of MRI brain (a) depicting cortical ribboning along bilateral frontal lobes (white arrow), insular cortex and right parieto-occipital cortex; and (b) electroencephalogram showing irregular sharp wave discharges with background diffuse slowing

During the further course of the hospital stay, the patient exhibited disorientation, behavioral changes including aggressiveness and irritability, myoclonic jerks, and rapidly progressed to akinetic mutism over a period of 2 weeks. Repeat brain MRI showed diffusion restriction along bilateral parieto-occipital lobes, frontal lobes, bilateral insular cortex, and bilateral corpus striatum [Figure 2a]. Repeat electroencephalogram showed characteristic periodic sharp wave discharges occurring at intervals of 0.8-1 seconds with a slow background [Figure 2b]. He was treated with one cycle of intravenous immunoglobulin (IVIg) 2 g/kg over 5 days, memantine 5 mg once daily, flupirtine 100 mg once daily, and melatonin 5 mg bedtime. The patient succumbed over the next 45 days.

Discussion

The present case report describes a rare presentation of sporadic Creutzfeldt-Jakob disease (CJD) with Alice in Wonderland syndrome as one of the early manifestations. Although visual symptoms, such as diminution of vision, hemianopia, macropsia, and micropsia, have been reported in Heidenhain variant of sporadic CJD, the occurrence of Alice in Wonderland syndrome is an unusual feature as in this case.[6] The diagnosis of probable sporadic CJD in the present case was based on the clinical presentation, elevated 14-3-3 protein in cerebrospinal fluid, characteristic EEG findings, and typical MRI changes. The clinical course of the disease was consistent with rapidly progressive dementia and myoclonus later culminating in akinetic mutism, which are typical features of CJD. According to the recent Centers for Disease Control and Prevention (CDC) diagnostic criteria of CJD, a "definite" diagnosis requires a positive brain biopsy, whereas "probable" CJD requires the presence of a neuropsychiatric disorder with positive real-time quaking-induced conversion (RT-QuIC) assays in CSF or the evidence of dementia with at least two of the four core clinical features (myoclonus, visual or cerebellar disturbance, pyramidal or extrapyramidal dysfunction, and akinetic mutism) and at least one of the three laboratory test (EEG, CSF 14-3-3, and brain MRI scan suggestive of CJD).[7]

Heidenhain variant of sCJD is characterized by early involvement of occipital cortex leading to visual symptoms at disease onset. The symptoms in AIWS basically localize toward the non-dominant posterior parietal and anterior occipital lobes.[8] There is a mismatch involving higher order neurons of visual association cortex (V4 and V5 of extra-striate cortex) and larger components of the visual network pathway.

The presentation of AIWS in CJD is not well known. Only a few scattered case reports are available, which are discussed herewith. The AIWS observed here is persistent and non-fleeting as evidenced from the case reports.

McGrath *et al*.[9] were the first to report a 64-year-old man who presented with a history of bilateral visual blurring and distortion, and incongruous left homonymous hemianopia of 4 weeks of duration. There was no evidence of altered sensorium, dementia, or myoclonus. Initial MRI brain scanning was unremarkable. EEG revealed regular 1-2 Hz generalized periodic discharges. A repeat MRI of brain was performed a few days later, which showed diffusion restriction in the form of cortical ribboning. CSF analysis revealed normal findings including a negative 14-3-3. Positron emission tomography scan of the brain showed right occipital hypo-metabolism. The patient was clinically diagnosed to be a probable case of Heidenhain variant of sporadic CJD (sCJD). Repeat CSF subsequently turned out to be positive for 14-3-3 protein and elevated t-tau protein (6301 pg/mL). The patient worsened rapidly and died at 4 months from the initial presentation. An autopsy was performed, and abnormal prion protein was detected using histo-pathological and immune-histochemical examinations, to confirm the diagnosis of sCJD.

Another 65-year-old man presented with a history of progressive confusion, visual hallucinations, photosensitivity, and the distorted appearance of objects and progressed to an unsteady gait and problems with spatial awareness of 2 weeks of duration.[10] Sooner, he developed features of frontal disinhibition and required assistance to walk. MRI of his

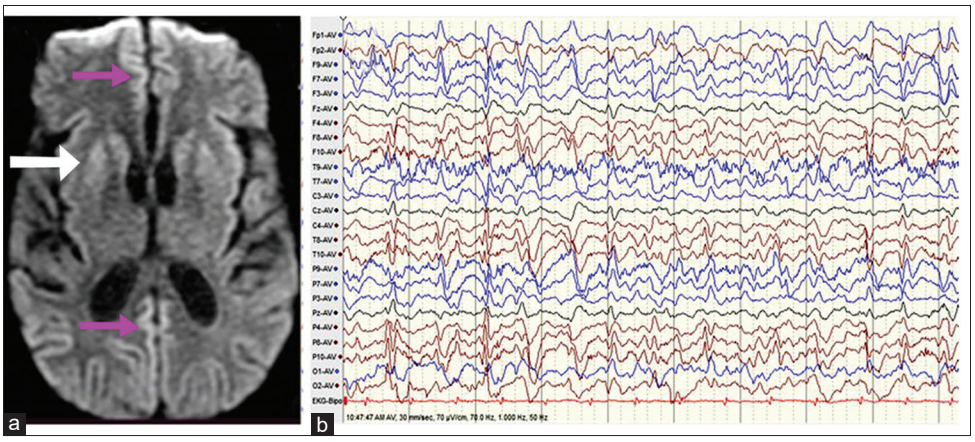

Figure 2: Axial DWI section of MRI brain (a) depicting cortical ribboning along bilateral parieto-occipital and frontal lobe (white arrow), bilateral insular cortex, and diffusion restriction in bilateral corpus striatum (pink arrow) and (b) electroencephalogram showing characteristic periodic sharp wave discharges (Rademecker complex)

brain showed increased signal restricted diffusion within the caudate nuclei bilaterally with further restricted diffusion of the cortex in the frontal, parietal, and occipital lobes on the right. An electroencephalogram demonstrated diffuse slowing and periodic sharp wave complexes. The real-time quaking induced conversion and protein 14-3-3 positive. During the following 10 days, he developed rigidity, hyper-reflexia, dystonic posturing of both upper limbs with frequent myoclonic jerks of his upper limbs. He had a fixed gaze with a restrictive horizontal gaze. The myoclonus and agitation were well controlled by a phenobarbital infusion. But he died within next 2 days.

The third and final case report described a 68-year-old male presenting with sudden-onset rapidly progressive visual distortion, in the form of akinetopsia, chloropsia, micropsia, macropsia, zoom vision, and time distortions.[11] It was sooner complicated by the development of new-onset paresthesias, instability of gait, aphasia, cognitive impairment, and abnormal behavior. He was finally diagnosed as sporadic CJD on the evidence of brain MRI changes and 14-3-3 protein in CSF. In the absence of any possible definitive therapy, the patient was discharged conservatively and he eventually succumbed to death within 2 months. The authors concluded that AIWS is sometimes detrimental, and CJD, although rare, should be considered an important differential, especially in the presence of rapidly progressive dementia.

Conclusion

CJD can present with visual symptoms initially and completely lack cognitive component, myoclonus, pyramidal, or extrapyramidal features. This case highlights the importance of considering the potential association between AIWS and CJD. Clinicians should be aware of the various presentations of AIWS and consider complete neurological evaluations, especially in patients with persistent or worsening symptoms. The prognosis of CJD per se is worse, but a high degree of clinical suspicion is prudent for correct diagnosis of this relatively uncommon disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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