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Hallucinatory palinopsia and paroxysmal oscillopsia as initial manifestations of sporadic Creutzfeldt-Jakob disease: A case study

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ABSTRACT

Background: Heidenhain variant of Cruetzfeldt Jacob Disease is a rare phenotype of the disease. Early and isolated visual symptoms characterize this particular variant of CJD. Other typical symptoms pertaining to muti-axial neurological involvement usually appear in following weeks to months. Commonly reported visual difficulties in Heidenhain variant are visual dimness, restricted field of vision, agnosias and spatial difficulties. We report here a case of Heidenhain variant that presented with very unusual symptoms of palinopsia and oscillopsia.

Case presentation: A 62-year-old male patient presented with symptoms of prolonged afterimages following removal of visual stimulus. It was later on accompanied by intermittent sense of unstable visual scene. He underwent surgery in suspicion of cataratcogenous vision loss but with no improvement in symptoms. Additionally he developed symptoms of cerebellar ataxia, cognitive decline and multifocal myoclonus in subsequent weeks. On the basis of suggestive MRI findings in brain, typical EEG changes and a positive result of 14-3-3 protein in CSF, he was eventually diagnosed as sCJD.

Conclusion: This case adds to the tally of handful reports of Heidenhain variant CJD in literature, particularly from India. Two atypical initial symptoms, namely hallucinatory palinopsia and paroxysmal oscillopsia were observed in the index case. Possible explanations of such phenomena in CJD have been explored in light of the available studies.

1. Background

Creutzfeldt-Jakob disease (CJD), characterized by tissue deposition of a misfolded form of the cellular prion protein (PrP^{sc}), is considered among the most fatal neurodegenerative disorders (Puoti et al., 2011). Depending on the mode of acquisition of prions, there are 3 types of CJD-sporadic, hereditary and acquired. Although a rare form of neurodegeneration, wide variability in clinical and pathological phenotype of this disorder has been observed. Heterogeneity in phenotype is actually inherent to the diagnostic criteria of CJD itself. Variable cortical; sub-cortical and cerebellar signs or their various combinations have been documented in different CJD registry across the globe. Different strains of prions, likely inscribed by alternative conformations of PrP^{sc},

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are considered the main reason behind this diversity. Additionally, the host variability in gene encoding PrP (PRNP) as determined in humans by polymorphisms or mutations also modulates the disease phenotype (Brown, Cathala, Castaigne, & Gajdusek, 1986; Krasnianski, Kaune, Jung, Kretzschmar, & Zerr, 2014; Parchi et al., 1999; Will & Matthews, 1984). Visual symptoms have been commonly reported in sporadic CJD (sCJD). However, even in early stages of the disease, they are often accompanied by other symptoms comprising of cognitive decline, extrapyramidal & pyramidal involvement, cerebellar ataxia and myoclonus.

Heidenhain variant of sCJD is well recognized but quite an uncommon phenotype in which visual symptoms not only predominate, but also precede the advent of other symptoms by at least weeks or months, reflecting the early targeting of prions to the occipital cortex. In a recent study consisting of a large series of sCJD cases, Bairadi et al. (2016) demonstrated the incidence of Heidenhain variant to be 4.9%. A comparable incidence (3.7%) of this particular phenotype was found by Cooper, Murray, Heath, Will, and Knight (2005) as well. However Kropp et al. (1999) reported a significantly higher value (20%), possibly related to the use of more liberal diagnostic criteria by them that did not emphasize on the temporal isolation of visual symptoms. The study by Appleby et al., despite applying strict criteria, reported a relative high incidence (17%) of Heidenhain variant.

Usual visual symptoms reported in Heidenhain variant of sCJD comprise of restricted visual field, visual blurring, cortical blindness, visual hallucinations and disturbed perception of colours or objects. Only a handful of cases reported in literature mention palinopsia as the initial manifestation in sCJD (Bairadi et al., 2016; Cooper et al., 2005; Purvin, Bonnin, & Goodman, 1989). Oscillopsia is another very unusual manifestation of Heidenhain variant sCJD.

We report here a case of sCJD of Heidenhain variant which presented with hallucinatory palinopsia and paroxysmal oscillopsia as the initial presentation that were followed by development of other typical features of sCJD (such as rapid cognitive decline, cerebellar ataxia and myoclonic jerks) after approximately 8 weeks.

2. Case presentation

A 62 year old Asian male patient hailing from rural part of Bengal (India) presented to us with complaint of visual difficulty over a period of 8 weeks. The patient was a musician by occupation and was continuing his work appropriately during the premorbid state. He used to make tunes for Bengali songs some of which were critically acclaimed as well. Around 2 months prior to presenting to us he was complaining to his son about a sense of visual oscillation which was intermittent and not restricted to any particular visual field. It was associated with a sense of nausea during the episode. At around the same time, he was also experiencing a peculiar visual phenomenon manifested by persistence of afterimage following a visual stimulus. Often he would complain that musical notes were visible to him around the room after he had completed playing a particular musical piece on some instrument. This would persist for minutes to hours sometimes but never more than a day. During these episodes, his sensorium was never altered and he never had any convulsive episodes. The images were mostly black and white (as in musical notes), stereotyped (mostly musical notations) and not restricted to any particular visual field. However, occasionally colored afterimages were also observed by him. This was accompanied by slow deterioration in his visual acuity over the subsequent 2–3 weeks. He was brought to an ophthalmologist who detected immature cataract in both his eyes and operated them in sequence within next 10 days. Following surgery, instead of improvement in visual acuity, his vision kept on deteriorating steadily. When he was brought to us that is at around 2 months following onset of his illness, he was already having significant visual dimness and mild unsteadiness of gait which was attributed to his falling visual acuity. Subsequently his unsteadiness in gait and stance increased with time followed by onset of cognitive decline (in the form of episodic memory impairment and visuo-spatial difficulties) and appearance of multifocal brief involuntary shock-like jerks as part of myoclonus. Physical examination findings revealed cerebellar ataxia and multifocal cortical myoclonic jerks. Detailed cognitive testing was suggestive of visuo-spatial difficulty and episodic memory impairments. Complex attention was also found to be deranged in our patient. His deep tendon reflexes were mildly exaggerated in both lower limbs accompanied by bilateral non-responsive plantar response, suggesting subtle pyramidal tract involvement.

Keeping in mind the multi-axial neurological involvement, differential diagnosis were formulated. An autoimmune process or a rapidly progressive neurodegeneration such as prion disease was our priority. However neuro-infections may also present themselves in such rapid course of illness. As he was investigated thoroughly, blood count and metabolic parameters were within normal limits. Anti TPO (Thyroperoxidase) antibody in serum turned out to be negative. Anti-nuclear factor was also negative. CSF cytology and biochemical parameters came within normal limits and culture was negative. Tests for syphilis, HIV (Human Immunodeficiency Virus), herpes simplex virus, human herpes virus-6, C-reactive protein, folate, vitamin B_{12}, erythrocyte sedimentation rate and homocysteine levels were all negative. Paraneoplastic markers in CSF also came to be negative.

Magnetic Resonance Imaging (MRI) of brain revealed bilateral caudate nucleus and putamen hyperintensity in T_2/FLAIR sequence as well as in diffusion weighted imaging (Fig. 1). Restricted diffusion was also observed in multiple cortical areas, mostly in occipital regions bilaterally, resembling ribbon pattern. Electroencephalogram (EEG) shows diffuse slowing of background activity with periodic sharp wave complexes along with intermittent triphasic waves (Fig. 2). Diagnosis was provisionally established based on the positive result of 14-3-3 protein detection in cerebrospinal fluid (CSF). No family history of CJD was available in our patient. Genetic testing could not be performed in this case. No recognized risk factor for acquiring CJD was present in our case. Therefore a diagnosis of probable CJD was assumed.

The prognosis and implications of being diagnosed with sCJD were duly communicated to the patient's caregiver while the patient continued to receive conservative management under the supervision of experienced neurologists (BKR and SD). Patient's relatives decided to give him domiciliary care

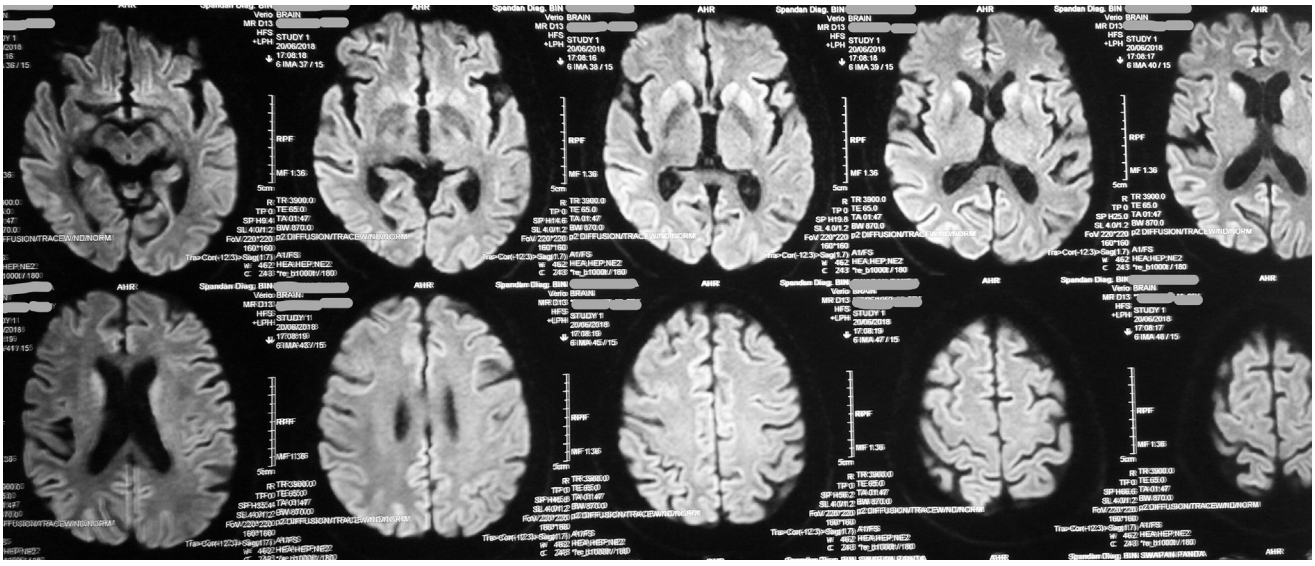

Fig. 1 – Patient's MRI. Bilateral caudate nucleus and putamen hyperintensity is observed, as well as multiple cortical areas resembling ribbon pattern.

through the terminal phases of his illness and subsequently he was lost to follow-up. Hence autopsy study was not available to us.

3. Discussion

Summarizing the case, our patient developed rapidly progressive visual difficulty as manifested in the form of palinopsia and oscillopsia accompanied by steadily falling visual acuity over a period of around 8 weeks which was followed by appearance of cognitive decline, cerebellar ataxia and multifocal cortical myoclonic jerks. Possible neuroinfections, structural lesions and auto-immune encephalitis were reasonably ruled out after thorough investigation. Brain imaging, however, raised suspicion of Prion disease which was further supported by typical EEG changes and positive 14-3-3 protein in CSF. A probable diagnosis of sCJD was made according to the current European diagnostic criteria (2010). Because the visual symptoms were early, prominent and

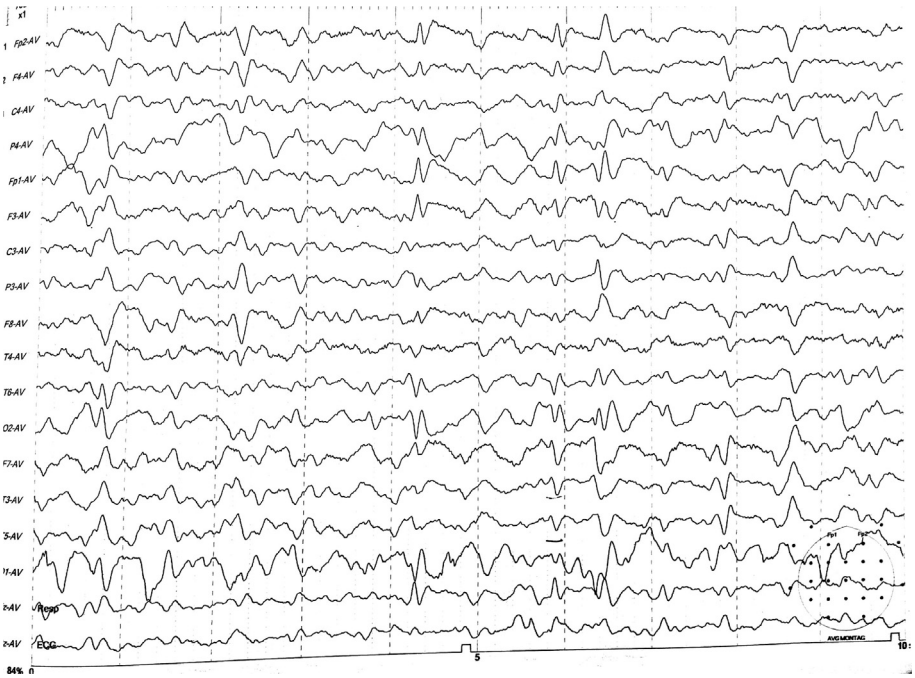

Fig. 2 – Diffuse slowing of background activity with periodic sharp wave complexes along with intermittent triphasic waves is observed.

preceded other symptoms by weeks to months, this was a typical case of Heidenhain variant of sCJD.

Although a rare phenotype of CJD, wide spectrum of visual symptoms have been reported in patients of Heidenhain variant. Palinopsia remains, however, one of the most under-reported symptoms of CJD till date. In the study by Cooper et al. that included 594 cases of sCJD over a span of 15 years, only 22 cases presented visual symptoms at the onset, of which a single case of palinopsia was reported. Bairadi et al. also in their large series of sCJD observed a lone case of palinopsia. The three large studies on sCJD from India by Mehendiratta et al., Chandra et al. and Biswas et al., do not have a specific mention of palinopsia as well. An autopsy study performed by Kher, Rao, Acharya, Mahadevan, and Shankar (2009) on a case of Heidenhain variant CJD, available in recent literature from India, does not mention this visual symptom either.

Palinopsia means abnormal persistence or recurrence of afterimage following removal of the visual stimulus. Recurrent images can persist immediately, return after sometime and may even last several hours. Reports are available in which the illusory image mixes with the current visual experience (Ardila, Botero, & Gomez, 1987). For instance, the first case of palinopsia, reported by Meadows and Munro (1977), in which they described an old lady who experienced hallucinatory palinopsia in the form 'Santa Clause beard' after a Christmas party. Later on, pathological autopsy revealed a lesion in the right occipito-temporal region in this lady. Gersztenkorn and Lee, in 2015, made a comprehensive review of all the palinopsia cases in literature and sub-divided this visual phenomenon into two basic types-illusory and hallucinatory. Illusory palinopsia refers to afterimages that are affected by ambient light and motion and are unformed, indistinct or low resolution. Hallucinatory palinopsia, on the other hand, describes afterimages that are formed, long-lasting and high resolution. The kind of palinopsia experienced by our patient fits typically with the description of hallucinatory palinopsia and was possibly consequent to the on-going degenerative process in the occipital cortex as well as its connections to the temporal cortex. The first reported case of isolated palinopsia due to CJD was by Purvin et al. (1989). In the paper by Bairadi et al. (2016), a male patient of 69 years age was documented to have palinopsia as early manifestation of sCJD (Heidenhain variant); however he had additional visual symptoms in the form of visual loss and visual field restriction. To that end, our case represents a genuinely rare clinical situation.

Oscillopsia, first reported by Brickner (1936), is an illusion of unstable vision comprised of the perception of to-and-fro movement of the environment. Based on the duration pattern, it can again be of two types-persistent and paroxysmal. Lesions in the oculomotor, vestibular and cerebellar systems are known to cause oscillopsia. The symptom of oscillopsia in our patient, however, was a curious observation because he did not have nystagmus or any demonstrable vestibular dysfunction to account for this early symptom of oscillopsia. Thus an alternate explanation must be sought for this particular phenomenology in the index case. Interestingly enough, a PET-activation study, more than 2 decades back, demonstrated de-activation of human visual cortex during involuntary ocular oscillation in humans (Wenzel et al., 1990). Hence theoretically, oscillopsia could also result from a deficit in mechanisms underpinning perceptual stability maintenance despite constant gaze displacement in the environment. The latter mechanism is known as 'spatial constancy' (Tilikete & Vighetto, 2011). After extensive research, the understanding of the mechanism of spatial constancy during and after eye movement still remains complex, supplemented by the more recent notion of visual attentional focus and salience maps. Combining the psychophysics experiments with neurophysiological recording of neurons has been helpful in determining the underlying neuronal network subserving aspects of spatial constancy. It included mainly the visual posterior sylvian area, just adjacent to the parieto-insular vestibular cortex (PIVC) (Dicke, Chakraborty & Thier, 2008). In humans, the neural network would involve cerebellar crus I, supplementary eye field and PIVC (Linder et al., 2006). Therefore it is within the realm of possibilities that in the presented case, the rapidly progressive degeneration of occipital cortex resulted in a deficient spatial constancy which manifested as so-called oscillopsia. Additionally, the subsequent inclusion of cerebellum in the disease process may have added to the sense of unstable visual scene.

A noteworthy observation in this case was the fact that our patient underwent cataract surgery prior to diagnosis, which would mean that only routine surgical precautions were employed during the procedure. Surgical intervention in a case of sCJD comes with presumable health hazards for the medical personnel because prion disease is transmissible. It is reported in literature that occasionally visual symptoms are so early and isolated in the temporal course of sCJD that is mistaken as an ophthalmological illness (S-Juan, Ward, Silva, Knight, & Will, 2004). The clinical scenario becomes particularly dubious when cataract is detected in such patients – a situation akin to 'being in the wrong place at the wrong time'. Our patient does not fit with possibility of iatrogenic CJD principally because the visual symptoms were unusual and the additional symptoms appeared almost immediately following the intervention leaving almost no scope for an incubation period. In addition, the investigation parameters also definitely pointed towards a diagnosis of sCJD. Therefore a more tenable situation would be that our patient was possibly harboring sCJD (Heidenhain variant) right from the beginning of his illness which was mistaken as catractogenous visual dimness. If that be the case, inadvertent exposure of the medical personnel to prions during surgical procedure can be assumed and it is not the first such case reported in literature (Gnanajothi, Umashanker, Vega, & Wu, 2013). Such events emphasize the importance of properly localizing lesions in patients with rapidly progressive visual dimness, particularly with symptoms as atypical as oscillopsia and palinopsia that occurred in the presented case. Raised awareness in this front can not only help avoid unnecessary surgical intervention for the patient but also reduce inadvertent exposure of the surgical team to prions even though cataract surgery is not yet an established risk factor for iatrogenic CJD as of now.

4. Conclusion

A rare phenotype of sCJD, namely Heidenhain variant, is reported here. Initial visual symptoms of palinopsia and

oscillopsia in sCJD have rarely been reported in literature previously which makes the index case a reportable one. Plausible explanations of such unusual visual phenomenon in this case of sCJD have been sought for in light of contemporary literature on this subject. The early and isolated appearance of visual symptoms in Heidenhain variant of sCJD can potentially force a diagnostic error on part of the ophthalmologist. CJD being a transmissible encephalopathy, possible hazards related to inadvertent exposure to prions during surgical procedure, particularly ophthalmologic intervention, need to be emphasized more in awareness campaigns.

Author's statement

The conditions of our medical ethics do not permit sharing of the raw MRI or EEG data supporting this case with any individual outside the author team under any circumstances.

CRediT authorship contribution statement

Durjoy Lahiri: Conceptualization, Methodology, Formal analysis, Resources, Writing - original draft, Writing - review & editing, Supervision. **Souvik Dubey:** Conceptualization, Methodology, Formal analysis, Resources, Writing - original draft. **Biman K. Ray:** Conceptualization, Methodology, Formal analysis, Writing - original draft. **Alfredo Ardila:** Conceptualization, Writing - original draft, Writing - review & editing.

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