Case report
Frontal lobe epilepsy with focal neuronal lipofuscinosis – Case report of a rare entity

Radhika Mhatre a, Sujit A. Jagtap b,c, Nilesh Kurwale c,d, Rashmi Santhoshkumar a, Yogeshwari Deshmukh e, Anita Mahadevan b,c*,

a Department of Neuropathology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India
b Department of Neurology, Bharati Vidyapeeth Medical College, Pune, Maharashtra, India
c Bajaj Allianz Comprehensive Center for Epilepsy Care, Deenanath Mangeshkar Hospital and Research Centre, Pune, Maharashtra, India
d Department of Neurosurgery, D.Y. Patil Medical College, Pune, Maharashtra, India
e Star Imaging and Research Centre, Pune, Maharashtra, India

1. Background

Focal neuronal lipofuscinosis (FNL) is a recently described entity seen in patients with frontal lobe epilepsy and is considered to be secondary to enhanced cellular autophagy [1]. Although associated with family history of seizures, the candidate gene and pathway underlying its pathogenesis remain unknown. There has been only a single study thus far reporting six cases of FNL [1], and we report the seventh case in world literature.

2. Case report

A 12-year-old right-handed girl with normal birth and development presented with seizures since one and a half years of age. She had focal impaired awareness seizures followed by focal to bilateral tonic–clonic seizures with secondary generalisation. Seizure frequency was one to two episodes per month. There was no history of febrile seizures in childhood or family history of seizures. She was receiving three anti-seizure drugs, carbamazepine 600 mg/day, lacosamide 250 mg/day, and clobazam 15 mg/day, and at the time of her evaluation, sodium valproate 800 mg/day and oxcarbazepine 900 mg/day were previously tried to control her seizures. Her neurological examination was normal. Neuropsychological testing was done pre-operatively as a part of presurgical evaluation. IQ assessment with the Malin's Intelligence Scale for Indian children (MISIC) [2] yielded low average verbal skills (VIQ = 85) with non-verbal skills placing in the borderline to low average range (PIQ = 77), although there was significant scatter in her profile. New learning and memory for verbal and visual information were in the low average range commensurate with estimates of her intellectual functioning. Visuo-perceptual skills and letter fluency were adequate. Areas of deficit included working memory, inefficient learning with repetition, and visuoconstruction (based on a block assembly task). Overall suggestive of fronto-parietal deficits. As she had drug resistant epilepsy, she underwent video electroencephalography (VEEG) which showed right frontal interictal epileptiform discharges and recorded two seizures of right frontal semiology and ictal onset. On Magnetic resonance imaging (MRI), the right superior frontal sulcus was deep, with blurring of grey-white junction, along with underlying white matter changes raising the possibility of right frontal dysplasia. Right frontal hypometabolism was noted on Positron emission tomography (PET).

Keywords: Dysmorphic neurons, Lipofuscin, Seizures, Autophagy
In view of clinico-electro-radiological concordance, she underwent resection of frontal dysplastic focus under image and electrocorticography guidance. Electrocorticography showed no spike on post-resection margin, suggestive of complete resection of dysplasia. Post resection MRI showed no residual dysplasia, and at one-year follow-up, she is seizure free and on carbamazepine 400 mg/day.

On histopathological examination, the cortical ribbon revealed full thickness dyslamination, most pronounced at the depth of sulcus. The entire cortical ribbon revealed large-sized hypertrophic neurons (approximately 50–100 μm), resembling dysmorphic neurons. The distended neurons revealed accumulation of intracytoplasmic granular material that was positive for Periodic acid–Schiff (PAS) and Luxol fast blue (LFB) and demonstrated autofluorescence, confirming it to be lipofuscin. In few neurons, the abnormal storage material extended into the axon hillock. On immunohistochemistry (IHC), non-phosphorylated neurofilament (SMI-32) showed a distinct ring-like pattern enclosing the lipofuscin aggregates and staining the peripheral marginalized intermediate filaments. It also highlighted the abnormal dendritic branching. Phosphorylated neurofilament (SMI-31), however, highlighted very few of these neurons, with a similar ring-like pattern. Few neurons revealed punctuate granular ubiquitin labelling. No labelling was seen with phosho-Tau and beta-amyloid. GFAP highlighted interspersed reactive stellate astrocytes. No balloon cells were seen on vimentin. Transmission electron microscopy of the dysmorphic neurons revealed intracytoplasmic, non-membrane bound, electron dense material with characteristics of lipofuscin (Fig. 2).

3. Discussion

Lipofuscin, the ‘wear and tear’ or the ‘ageing pigment’, is a highly crosslinked nondegradable aggregate comprising of oxidised proteins and lipids, carbohydrates, and trace amounts of metals (particularly iron) [3,4]. It is formed by peroxidation within lysosomes following autophagocytosis. Ultrastructurally, lipofuscin is electron dense, non-membrane bound material having granular, homogeneous, lamellated, or compound appearance [5]. Accumulation of lipofuscin in FNL is attributed to enhanced autophagy [1].

Liu and colleagues first described this entity in 2016, in a study of 20 cases of focal drug resistant frontal lobe epilepsy. They reported 6 cases with the specific pathology of FNL that are reviewed in Table 1. This report describes the neuroimaging, the electrophysiology, the proteome, of this entity, and the involvement of mTOR and autophagic pathway. We report the seventh documented case of FNL with clinical, imaging, histopathology, and ultrastructural details. Liu et al. proposed the term “dysmorphic neurones with lipofuscin (DN/L)” to refer to these abnormal neurons. Proteomic analysis of the DN/L using laser capture microdissection found upregulation of the proteins clathrin, dynamin-1, adaptor protein-2 (AP2), synapsin, syntaxin, synaptotagmin, and vesicle-associated membrane proteins which have roles in autophagy, phagosome, and lysosomal pathways, akin to that seen in aged and Alzheimer disease human brains. Family history of seizures was recorded in half of the reported cases (3/6), albeit absent in our patient.

MR imaging abnormalities has been recorded in 5 of 6 reported cases, as blurring of grey-white margin with subtle cortical signal intensity changes. No obvious associated white matter hyperintensity or trans-mantle sign has been noted in these cases [1]. In our case, there were unique findings on MRI with a peculiar ‘gyriform pattern’. On T2W and FLAIR images, the cortex of right superior frontal sulcus was slightly hyperintense with hypointensity of immediately subjacent subcortical white matter producing a blurred grey-white matter junction. The white matter beneath this showed linear hyperintensity along the subcortical zone coproducing a peculiar ‘gyriform’ pattern as opposed to the transmantine sign seen in focal cortical dysplasia IIb (FCD type IIb). This alternating hypertensive cortex, relatively hypointense blurred grey-white matter junction and ‘gyriform’ hyperintensity in the subcortical white matter conferred a ‘multi-layered’ appearance of the affected gyrus. In FCD IIb, MRI most often reveal widening of cortex, blurring of the grey-white matter junction with associated hyperintense signal in the underlying white matter on T2 weighted/FLAIR images, and the ‘transmantle sign’ on T2 FLAIR imaging characterised by a funnel-like hyperintensity tapering from the gyrus to the ventricle. Such ‘gyriform’ white matter hyperintensity and ‘multi-layered’ appearance of affected gyrus may prove to be an imaging biomarker for diagnosis of this entity, but needs validation in more cases. The hyperintensity of the cortex on T2W/FLAIR may be produced by accumulation of lipofuscin within the swollen neurons.

FNL and FCD are close mimics both clinically and on neuroimaging. Distinction of FNL from FCD currently mandates histological examination. FCD spectrum comprises malformation of brain with cortical dyslamination and cytoarchitectural changes [6]. At present, there are nine subtypes of FCD. Of these, FCD type Ila and IIb mimc FNL due to the presence of dysmorphic neurons. However, they do not show the excess lipofuscin or the peculiar ring-like staining with neurofilaments. The DN/L is limited to the cortical layers and is not drawn into the white
matter unlike the characteristic balloon neurons of FCD IIb. FCD type II has been associated with the distinct activation of the mTOR signalling pathway with impaired autophagy. In contrast to FNL, there is enhanced autophagy, and markers of mTOR pathway are infrequently detected in the cases studied [1,7].

Another condition characterised by accumulation of lipofuscin within neurons and various organs is the neurodegenerative lysosomal storage disorder, Neuronal ceroid lipofuscinosis (NCL). Lipofuscin is the term used for ageing pigments, whereas ceroid is used to describe pathologically derived storage material [3]. NCL has distinctive clinical presentation with seizures, ataxia, myoclonus, developmental problems, visual loss, behavioural changes, and cognitive decline depending upon the type and the age at onset. Neurons in NCL are distended with ceroid or lipofuscin-like lipopigment with similar biochemical staining characteristics and autofluorescent property identical to FNL. However, they are associated with additional neuropathological findings such as marked diffuse atrophy of the cerebral cortex, severe depletion of the neurons, secondary degeneration of white matter with astrogliosis, and microglial activation. At ultrastructural level, this storage material consists of characteristic membrane bound inclusions containing granular osmiophilic deposits, curvilinear, rectilinear, and fingerprint profiles [8]. Despite histological similarity, FNL is easily distinguished from NCL based on clinical grounds, with NCL being a diffuse and multisystem disorder. Our case did not have any cognitive decline or intellectual impairment and had frontal lobe epilepsy with focal lesion on MRI imaging.

Clinical outcome in the six cases reported is variable, and 4/6 had poor outcome as per 2001 ILAE classification by Wieser et al. [1,9] (Table 1). Our case, however, had good outcome of class 1a and is seizure free at one-year follow-up. The follow-up in reported cases is, however, longer (range: 1–6 years), and it remains to be seen if our patient continues to do well.
The post-surgical outcome utilises the ILAE classification [9]. DN/L = dysmorphic neurones with excess lipofuscin, L = left, R = right, N/A = not available.

4. Conclusion

Frontal lobe epilepsy with focal neuronal lipofuscinosis is a rare entity that closely mimics focal cortical dysplasia and is amenable to epilepsy surgery. Though rare, this entity needs to be kept in mind particularly because of less favourable post-operative outcomes and association with family history of seizures.

Ethical statement

The work described has been carried out in accordance with the Code of Ethics of the World Medical Association. Informed consent was obtained from the subject in the case report.

Declaration of competing interest

None of the authors have any conflict of interest to declare.

References

[1] Liu JY, Reeves C, Diehl B, Coppola A, Al-Hajri A, Hoskote C. Early lipofuscin accumulation in frontal lobe epilepsy. Ann Neurol. 2016;80:882–95.
[2] Malin AJ. Malin's intelligence scale for children. Indian J. Ment Retard. 1971;4:15–25.
[3] Seehafer SS, Pearce DA. Do you say lipofuscin, we say ceroid: definition and use. Neurobiol Aging. 2006;27:576–88.
[4] T1 Jung, Bader N, Grune T. Lipofuscin: formation, distribution, and metabolic consequences. Ann N Y Acad Sci. 2007;1119:97–111.
[5] Terman A, Brunk UT. Lipofuscin: mechanisms of formation and increase with age. APMIS. 1998;106:265–76.
[6] Blumcke I, Thoms M, Aronica E, Armstrong DD, Vinters HV, Palmini A. The clinicopathologic spectrum of focal cortical dyslamias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia. 2011;52:158–74.
[7] Najm IM, Sarnat HB, Blumcke I. Review: the international consensus classification of focal cortical dysplasia - a critical update 2018. Neuropathol Appl Neurobiol. 2018;44:18–31.
[8] Walkley SU, Suzuki K, Suzuki K. Lysosomal diseases. In: Love S, Perry A, Ironside J, Budka H, editors. Greenfield’s neuropathology. 9th ed. United States: CRC press; 2015. p. 439–522.
[9] Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia. 2001;42:262–6.