

# Glioneuronal hamartoma with unusual clinical manifestations in a case of pharmacoresistant temporal lobe epilepsy

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## Citation

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## Abstract

Epilepsy is a common and serious chronic neurological disorder, with pharmacoresistance occurring in up to one third of cases of epilepsy. Temporal lobe is the most frequent site of epileptogenic lesions, and surgically resected specimens from patients with pharmacoresistant epilepsy reveal a broad spectrum of lesions, with hippocampal sclerosis as the most common pathology while glioneuronal hamartoma is a rare entity. We report a case of a 62 year-old woman with chronic pharmacoresistant epilepsy characterized by an unusual clinical picture of complex, partial and generalized tonic-clonic seizures with associated repetitive back and forth pelvic movements, not clinically typical for temporal lobe epilepsy. However, video EEG monitoring, MRI, and brain SPECT revealed a right temporal lobe epileptogenic focus. Temporal lobectomy was performed and revealed glioneuronal hamartoma in the white matter, characterized by the presence of immature oligodendroglial-like cells, dysmorphic/dysplastic small neuronal cells, and hybrid cells with intermediate morphology in a hypomyelinated fibrillar background. No proliferative activity was present. Immunostain for CD34 highlighted intense bush-like ramifications of the cell processes in the dysplastic glioneuronal cells. The patient remained seizure free during the follow-up period of 32 months. Our case is noticeable for atypical clinical features of temporal lobe epilepsy, associated with the rare entity of glioneuronal hamartoma composed of an unusual immature cellular composition with CD34 positivity.

## INTRODUCTION

In pharmacoresistant epilepsy (PRE), surgery has been established as an effective mode of therapy, and has contributed to providing tissue samples for studying the spectrum of lesions associated with PRE. The lesions may include Ammon's horn sclerosis, tumors and malformations.[1] Intracerebral glioneuronal hamartoma represents a rare cause of PRE encountered in less than 2% to 3.2% of surgical specimen, in reported studies comprising of relatively large number of patients. [2-4] We present a case of glioneuronal hamartoma of the temporal lobe from a patient with a longstanding history of PRE, associated with an unusual clinical picture, and an unusual histological profile of immature cellular composition. Also, a brief review of the causes of PRE in the literature is discussed.

## CASE REPORT

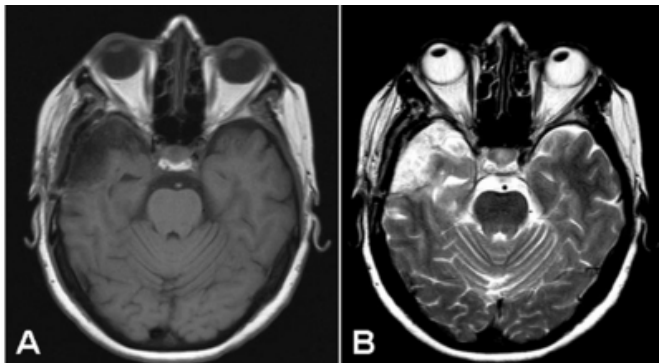
Case report pertains to a 62 year-old woman with history of refractory epilepsy from the age 26, characterized by complex partial seizures (CPZ) and generalized tonic-clonic seizures. The seizures were preceded by an aura of

epigastric pain followed by complex seizures in which she started counting and walking back and forth. Medical therapy (lamictal) reduced the frequency of CPZ from 8-9 times per month to 2-3 times every 6 months. However, the frequency of CPZ progressively increased in the last few years. Side-effects of medication (ataxia and tremors) were also troublesome. During her angiogram for WADA test in an outside institution, she had stroke which fortunately resolved with no residual deficits. Past medical history was also significant for depression and hypercholesterolemia.

Although, the repetitive back and forth pelvic movements were not clinically typical for temporal lobe epilepsy (TLE), video EEG monitoring disclosed a right temporal lobe focus. The MRI revealed a lesion in the right hippocampus with hypointense signal on T1, and increased signal intensity on T2 weighted image, (Figure 1A&B). Brain SPECT (ictal and inter-ictal) confirmed the right temporal epileptogenic focus.

**Figure 1**

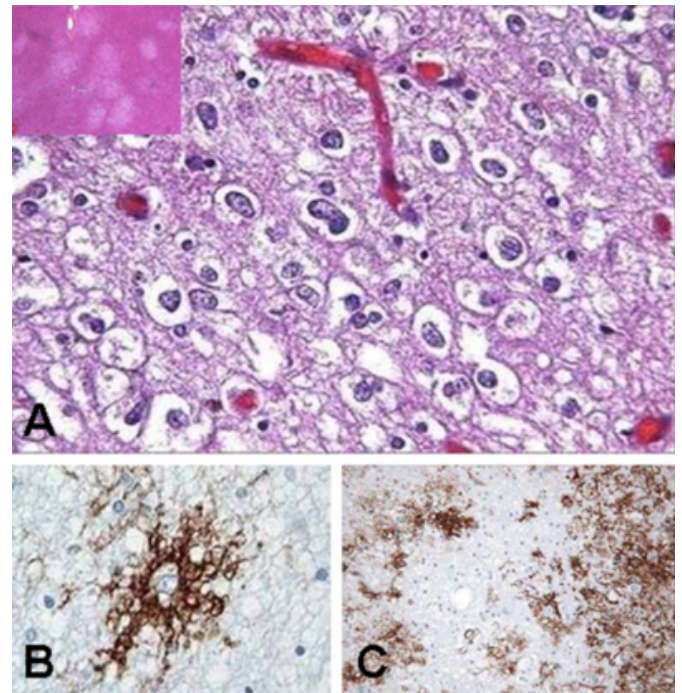
Figure 1: A. MRI of brain showing a lesion with hypointense T1 signal in the right anterior temporal lobe; B. Hyperintense T2 signal in the right anterior temporal lobe



The patient underwent a partial right temporal lobectomy. Biopsies from the temporal lobe were sent for intraoperative frozen sections and did not show any evidence of tumor. Segment of anterior temporal lobe was resected up to 4.5 cm from the tip and sent to pathology. The specimen consisted of a 4.5 x 4.0 x 1.5 cm portion of cortex and white matter. The cortical surface showed unremarkable gyral pattern with smooth glistening meninges. On serial sectioning at 3-4 mm interval, the cortical ribbon was regular with average 3 mm thickness. There was a single lesion in the deep white matter measuring up to 1.2 cm and composed of multiple foci of soft grey-tan areas. The specimen was submitted in-toto for microscopic examination, and revealed within the 1.2 cm grossly defined area, multiple micronodular to ill-defined foci (Figure 2A inset), composed of a mixture of small neuronal-like cells and immature oligodendroglial-like with hybrid cells of intermediate morphology, in a hypomyelinated background (Figure 2A). The neuronal-like cells showed dysmorphic/ dysplastic features including occasional binucleation and nuclear membrane convolutions. CD34 immunostain (stem cell marker transiently expressed during early neurulation) highlighted bush-like intense ramifications of cell processes of dysplastic glioneuronal cells scattered singly or in clusters (Figure 2B & C). Chromogranin staining was equivocal in these dysplastic/ dysmorphic neurons. No Ki-67 proliferative activity or bcl-2 immunoreactivity was seen. Background staining of the neuropil appeared unaltered for -100 protein, however, neuropil staining for synaptophysin and neurofilament appeared to be decreased in these areas compared to the surrounding white matter. GFAP highlighted reactive astrocytosis, more prominent in the white rather than the gray matter.

**Figure 2**

Figure 2: A. Multiple ill-defined foci in the white matter formed of a mixture of small dysmorphic/ dysplastic neuronal-like cells and immature oligodendroglial-like cells with hybrid cells of intermediate morphology in a hypomyelinated background (inset, low power). B & C. CD 34 immunostain highlights bush-like intense ramification of cell processes of glioneuronal cells, which were individually scattered (B) or in clusters (C). (Hematoxylin and Eosin stain: A. 400x; inset 25x, CD34 immunoperoxidase stain: B. 400x & C. 40x).



Calretinin stained frequent neurons in the cortex and occasionally in the white matter, interpreted as GABA inhibitory neurons, but no appreciable staining was noted in the lesions. Other findings included heterotopic neurons scattered in the deep white matter and occasionally in the molecular layer of the cortex, Chaslin's gliosis and hyaline thickening of small blood vessels. No balloon cells or Ammon's horn structure of the hippocampus were present. The diagnosis of subcortical glioneuronal hamartoma was rendered. Due to the unusual and complex nature of the lesion an expert neuropathology opinion was consulted from an outside institution, the consulting pathologist concurred with the diagnosis and made the following comment: "This is a most unusual case, even among the many corticectomies for seizure disorder that we encounter and the immunohistochemical profile of the hamartomatous lesions is also most unusual". After surgery, the patient has been seizure free during the follow-up period of 32 months.

## **DISCUSSION**

Study of temporal lobe resections from patients with PRE, revealed structural lesions in up to 97.2% of cases [3], and in extra-temporal lobectomies structural lesions were seen in 86% of cases [5]. In the remaining cases either non-specific pathology or no pathologic lesion was identified at microscopic examination. In cases with lack of identifiable lesion the cause of epilepsy may be attributed to changes at a cellular or biochemical level which was not possible to detect by light microscopy or alternatively the origin of epilepsy may reside elsewhere. However, the reported incidences may be affected by selection bias as patients with an identifiable focal lesion in the temporal lobe on imaging studies are more likely to be offered the surgical treatment option for temporal lobectomy.

The spectrum of identifiable lesions associated with PRE in resected specimens include hippocampus sclerosis, neoplasms, malformative lesions, inflammatory, post-traumatic/ postoperative lesions or remote ischemic/ infarctive changes. [1,2, 3,6] Most resections for PRE tend to involve the temporal lobe and hippocampus sclerosis is the most commonly associated lesion followed by tumors and malformative lesions [3,7].

Glioneuronal hamartomas (GNH) of the central nervous system are rare, varying from less than 2% to 3.2% of PRE cases. [2-4] GNH are defined as focal defect in tissue organization during development and cell migration. [8] GNH may be intracerebral, or intracranial but extracerebral or even extracranial [9-11]. Extracerebral hamartomas probably originate from an aberrant development of the neuronal tube, while intracerebral hamartomas most often encountered in the region of the hypothalamus but may be cortical or even subcortical and located in different lobes of the brain, are probably caused by aberrant migration or incomplete differentiation of embryonic neuroepithelium.

GNH is distinct from cortical dysplasia by being a circumscribed disorganized collection of glial cells characterized by a circumscribed disorganized collection of glial cells primarily astrocytes admixed with a neuronal component. Glioneuronal hamartoma and hamartias are histologically similar. However, the term glioneuronal hamartoma is used for grossly visible lesions more than 10 mm in size (as in our case, also see radiological appearance Figure xx), and the term hamartia is used for small or microscopic lesions (0.2 to 10mm) that are not identifiable grossly or on radiologic examination [2]. The neuroglial

tissue in hamartoma is usually mature, however, in our case the neuroglial cells were immature with hybrid-like cells displaying intermediate morphology between neural and glial cells. Eosinophilic granular bodies, microcalcification and small blood vessels proliferation may also be seen in GNH. The absence of necrosis, mitosis, infiltrative pattern or prominent cytological atypia distinguishes hamartoma from neoplasms causing epilepsy. [12] Glioneuronal hamartomas are frequently associated with microscopic cortical dysplasia in the adjacent brain tissue. This association is in line with their developmental nature. In the majority of the reported cases surgical resection is successful in getting rid of epileptic seizures, despite the fact that frequently cortical dysplasia is seen in the surrounding brain tissue, part of which may not have been removed surgically.[13]

In our case, CD34 immunoreactivity highlighted bush-like intense ramifications of cell processes of dysplastic glioneuronal cells, scattered singly or in large clusters. CD34 is a stem cell marker transiently expressed during early neurulation. It has been speculated that in PRE, CD34 expression points to origin of these cells from dysplastic or neoplastically transformed precursor cells. [2] The CD34 immunoreactivity and co-expression of glial and neuronal markers in varying number of these cells suggests failure of these cells to commit to a final specific phenotypic differentiation. Other studies noted CD34 immunoreactivity in FCDs, in majority of gangliogliomas, rare cases of pleomorphic xanthoastrocytoma, and complex form of dysmorphic neuroepithelial tumors associated with PRE. [1,14] Thus a common histogenic origin of these lesions from CD34 positive precursor cells which undergo abnormal glioneuronal differentiation was proposed.

In conclusion, intracerebral glioneuronal hamartoma is a rare entity that may be associated with PRE. In the majority of the reported cases cessation of seizures occurs after surgical resection of hamartoma, despite the frequent presence of cortical dysplasia in the surrounding brain tissue. The histological distinction of this rare entity from other developmental lesions and tumors may be difficult on histological examination, particularly in cases of immature/ dysplastic cellular composition as in our case. The circumscription of the lesion, absence of proliferative activity and significant cytological atypia are helpful distinctive features in classifying the lesion as glioneuronal hamartoma.

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