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BRIEF COMMUNICATION

Subcortical axonal loss with glial reactions following partial status epilepticus with neuroradiological findings of reduced subcortical diffusion

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Abstract

Hyperintensity in the subcortical white matter on the diffusion-weighted magnetic resonance image has been described recently, in association with partial status epilepticus. Although this reduced subcortical diffusion is typically seen in patients with acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), the exact pathophysiological mechanism is unclear. We report the case of a 3-month-old boy who underwent surgery for intractable epilepsy associated with cortical dysplasia in the left peri-Rolandic area, coincident with the appearance of reduced subcortical diffusion. Neurohistological findings revealed that the most prominent finding was axonal loss with marked astroglial and microglial reactions in the white matter. Neither degenerated neurons nor neurophagocytic microglial accumulation was evident in the cortex. These findings confirm that white matter can be secondarily damaged in patients with partial status epilepticus, and possible pathomechanism of reduced subcortical diffusion is discussed.

Keywords Bright tree appearance · Astroglia · Microglia · Partial status epileptics

Introduction

Hyperintensity in the subcortical white matter (termed bright tree appearance) on diffusion-weighted image (DWI) had been described in association with prolonged seizure as observed in cases of partial status epilepticus (SE) and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [1]. The exact pathophysiological mechanism is still unclear, and histopathological data is limited. Two recent literature reported inconsistent pathological findings, one involving axonal [2], while the other cortical changes [3]. We describe a 3-month-old boy who underwent surgery for intractable epilepsy associated with cortical dysplasia (CD) in the left peri-Rolandic area, when reduced subcortical diffusion was noted.

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Clinical summary

A 3-month-old boy was admitted for intractable epilepsy. At the age of 10 days, he began to develop daily partial seizures of his right face and upper limb. The seizure frequency gradually increased and secondary generalized seizures occurred by 3 months.

On admission, his seizures occurred 20–30 times a day and each seizure lasted for 1 min. Long-term electroencephalography (EEG) monitoring showed that repeated ictal discharges began at the left central region and spread to the contralateral side (Fig. 1a). MR images revealed diffuse cortical thickness,

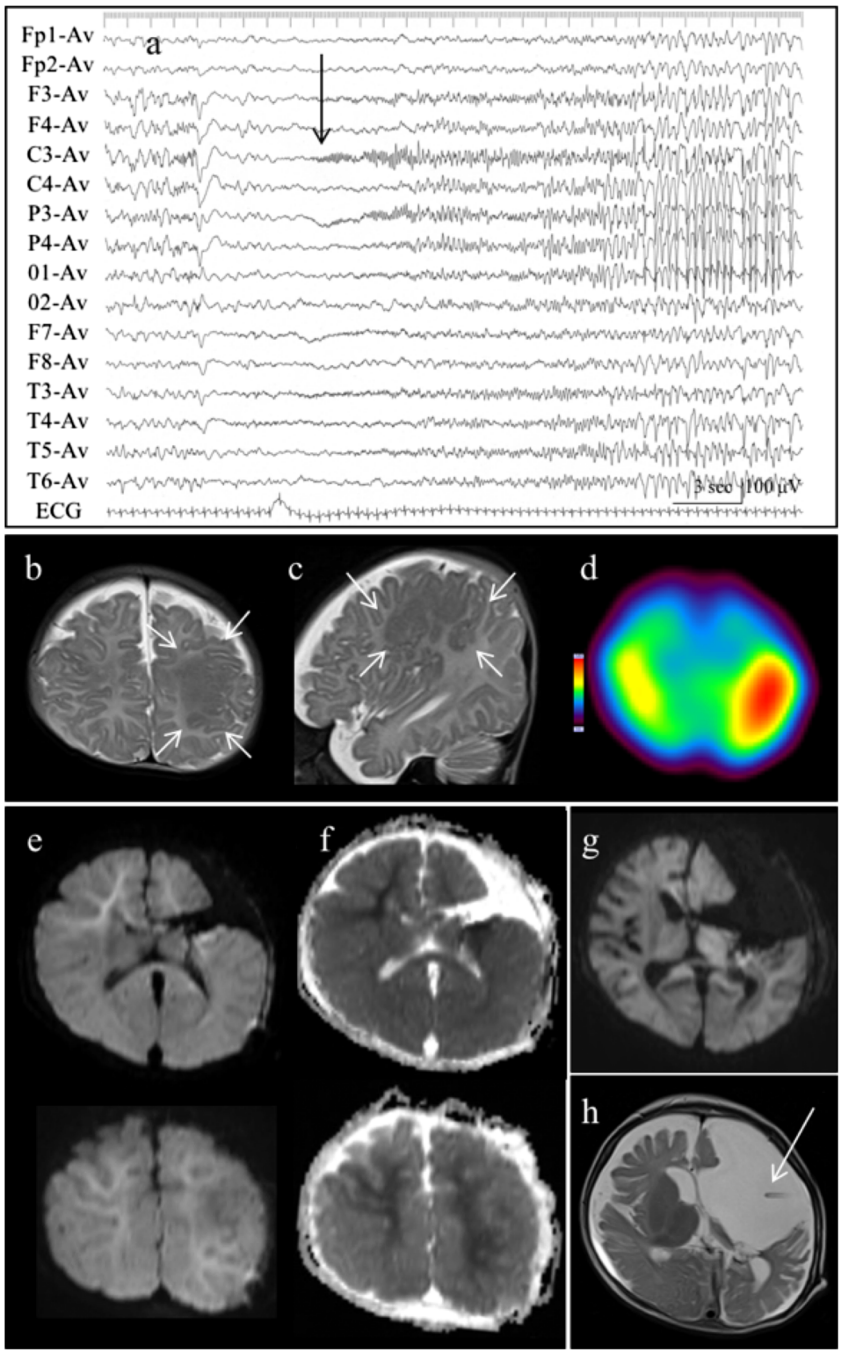

Fig. 1 **a** Electroencephalography (EEG) with averaged reference (Av) showed that repeated ictal discharges began at the left central region (C3 in International EEG 10–20 System; black arrow) and spread to the contralateral side. **b**, **c** Axial and sagittal views of T2-weighted magnetic resonance imaging (T2WI) on admission revealed diffuse cortical thickness at the left peri-Rolandic area (white arrows). **d** Single-photon emission tomography with 123I-iomazenil in the early phase showed increased uptake in the area corresponding to the hypointense area on T2WI. **e** Diffusion-weighted image (DWI) performed just after the operation showed a high intensity area in the subcortical white matter of the bilateral frontal lobes. The cortical dysplasia lesion in the left peri-Rolandic area was not involved with surgical manipulation. **f** The apparent diffusion coefficient (ADC) map showed low intensity lesions in the same area. **g** DWI on postoperative day 8 confirmed the disappearance of reduced subcortical diffusion, but diffuse cerebral atrophy was noted. **h** T2WI at postoperative month 5 showed marked cerebral atrophy. The white arrow indicates the catheter of the subdural-peritoneal shunt

indicating CD at the left peri-Rolandic area (Fig. 1b, c). Single-photon emission tomography with 123I-iomazenil (IMZ-SPECT) at the early phase showed increased uptake in the corresponding area (Fig. 1d).

In spite of oral administration of phenobarbital, levetiracetam, as well as intravenous midazolam and fosphenytoin, his seizures were not controlled. Barbiturate coma therapy with thiamylal sodium was performed. EEG during the barbiturate coma showed frequent electrical seizure activities at C3 despite suppressed activities at the other electrodes.

With the limitations of medical treatment, epilepsy surgery was indicated. On day 15, a left hemispherotomy was performed through a surgical window in the frontal lobe as an access route to the lateral ventricle. A computed tomographic scan performed just after the operation revealed swelling in the bilateral cerebral hemispheres. Subsequent MR images showed reduced subcortical diffusion in bilateral frontal lobes (Fig. 1e, f). Therapeutic hypothermia was performed. Follow-up MR images on postoperative day 8 confirmed the disappearance of reduced subcortical diffusion, but diffuse cerebral atrophy was observed (Fig. 1g).

During postoperative follow-up for 6 months, he remained free from seizures with phenobarbital and phenytoin administration, although mental retardation was observed. Follow-up MR imaging demonstrated marked cerebral atrophy (Fig. 1h). External hydrocephalus was controlled with a subdural-peritoneal shunt.

Pathological findings

Histopathological examination revealed normal cortical lamination without apparent dysgenetic neurons and balloon cells on hematoxylin and eosin (HE) staining, and immunostaining for neuronal nuclear antigen (NueN) and vimentin indicating

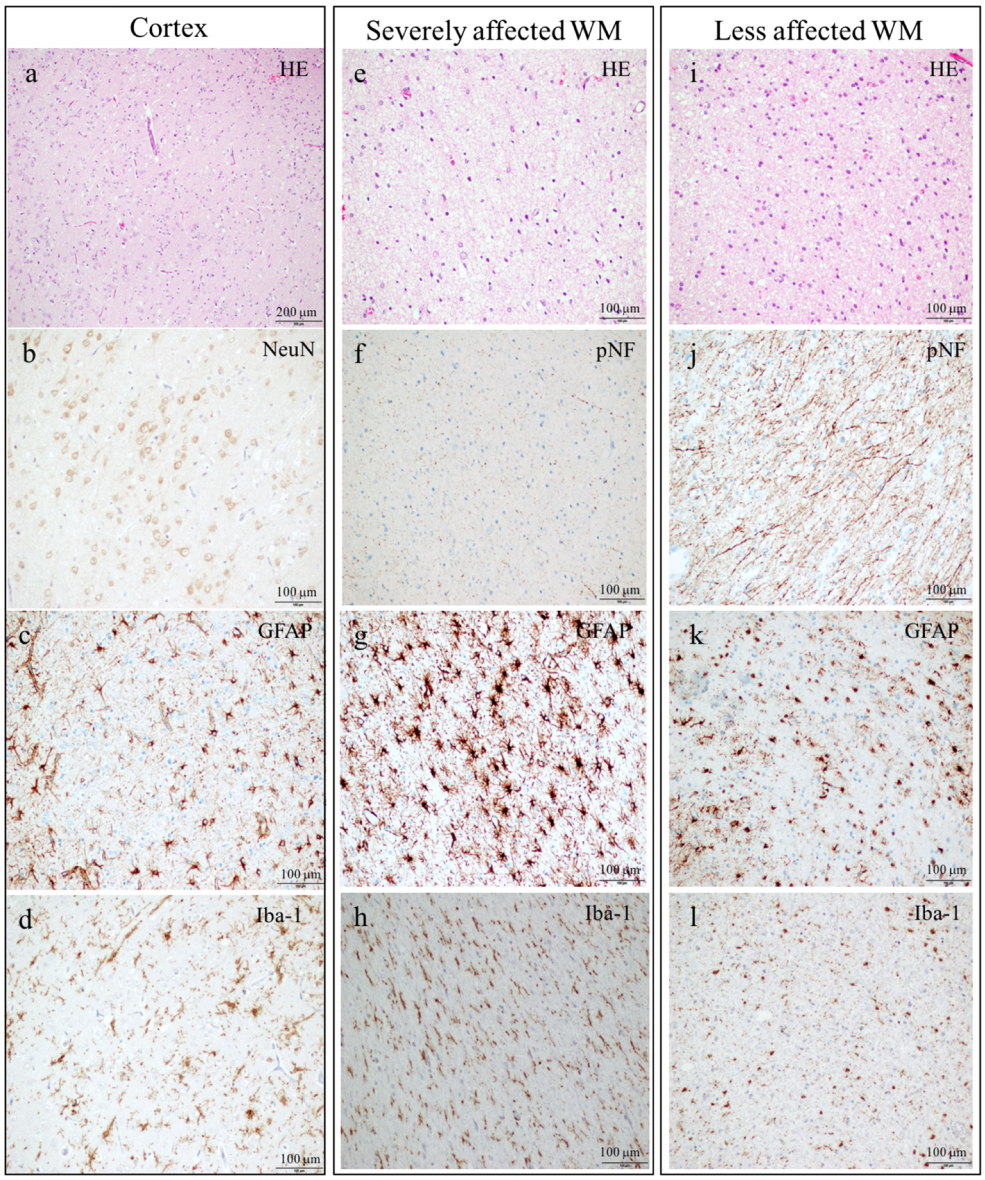

Fig. 2 **a**–**d** Photomicrographs of the cortex with hematoxylin and eosin (HE) staining (**a**) and immunostaining for neuronal nuclear antigen (NueN) (**b**), glial fibrillary acidic protein (GFAP) (**c**), and ionized calcium-binding adapter molecule-1 (Iba-1) (**d**). The number and morphology of the neuronal cells were mostly preserved and degeneration of the neuronal soma was not evident (**a**, **b**). Although GFAP-immunopositive reactive astrocytes (**c**) and Iba-1-immunopositive reactive microglia were observed, neurophagocytic microglial accumulation was not observed (**d**). **e**–**h** Photomicrographs of the severely affected part of the white matter (WM) with HE staining (**e**) and immunostaining for phosphorylated neurofilament (pNF) (**f**), GFAP (**g**), and Iba-1 (**h**). Rarefaction of the tissue with glial reactions was observed (**e**), with severe loss of pNF-positive axons (**f**). In these areas, more prominent reactions of GFAP-positive astrocytes (**g**) and Iba-1-positive microglia (**h**) were observed, compared with the cortex. **i**–**l** Photomicrographs of the less affected WM with HE staining (**i**), showing relatively preserved pNF-positive axons (**b**). GFAP-positive reactive astrocytes (**k**) and Iba-1-positive reactive microglia (**l**) were also observed, but in considerably lower numbers compared with the severely affected area (**e**–**h**). Scale bars: 200 μm in a; 100 μm in b–l

that the CD lesion was not included in the specimen (Fig. 2a, b). The number and morphology of the neuronal cells in the cortex were mostly preserved and degenerated features were not evident (Fig. 2a, b). Although glial fibrillary acidic protein (GFAP)-immunopositive reactive astrocytes (Fig. 2c) and ionized calcium-binding adapter molecule-1 (Iba-1)-immunopositive reactive microglia (Fig. 2d) were observed in the cortex, neurophagocytic microglial accumulation was not observed.

In contrast, most parts of the white matter showed rarefaction of the tissue with intense glial reactions (Fig. 2e). Marked axonal loss was demonstrated by immunostaining for phosphorylated neurofilaments (Fig. 2f). More prominent astrocytic and microglial reactions than those seen in the cortex were revealed by immunostaining for GFAP and Iba-1, respectively (Fig. 2g, h). A small part of the white matter was less affected (Fig. 2i), with relatively preserved neurofilament-positive axons (Fig. 2j) and considerably smaller numbers of GFAP-positive reactive astrocytes and Iba-1-positive reactive microglia (Fig. 2k, l).

Discussion

The most prominent histological finding of this patient was the axonal loss in the rarefied white matter. Neither degenerated neurons nor neurophagocytic microglial accumulation was evident in the cortex. Another conspicuous finding was marked astroglial and microglial reactions in the white matter, rather than in the cortex. Our findings indicate that the primary pathological change seen during the characteristic bright tree appearance reflected axonal changes. Clinical entities with resembling neuroradiological finding of reduced subcortical diffusion include viral encephalitis, and certain types of metabolic encephalopathies. However, laboratory and pathological investigations ruled out these differential diagnoses.

Based on the electroradiological findings, the epileptogenic lesion in the present case was thought to be CD with highly "intrinsic" epileptogenicity [4]. The CD lesion was not histologically proven because the surgical window was placed on the left frontal lobe rostral to the lesion. Increased uptake on IMZ-SPECT was observed, suggesting that "ictal" hyperperfusion induced by intrinsic epileptogenicity was present during the clinical interictal state. Furthermore, barbiturate coma therapy failed to suppress the electrical seizure activities at the left central region. These findings indicate that the epileptogenicity of the lesion might have sufficient intensity to induce excitotoxic injury.

The epileptogenic cortex during partial SE is in an electrophysiologically extreme states, in which induction of glutamate excitotoxity and flow-metabolism uncoupling can occur, leading to cytotoxic edema [5]. There is growing evidence that glutamate excitotoxicity can be considered a major cause of axonal degeneration in white matter diseases [6]. Induction of glutamate excitotoxicity by SE may result in axonal damage. Most of the reported cases who developed reduced subcortical diffusion following partial SE are infantile cases. Immature myelination and hence white matter vulnerability might cause the regional specificity seen in these cases.

Under excitotoxic conditions, astrocytes are thought to play a neuroprotective role by removing and metabolizing extracellular glutamate [7]. Excessive glutamate uptake induces an increase in astrocytic cell volume, as histologically demonstrated in the white matter of our case.

Our findings provide neuropathological evidence that subcortical axonal loss with marked astroglial and microglial reactions form the basis of pathophysiological mechanism seen in the so-called "bright tree appearance" lesion. Similar pathological finding of reactive astrocytes with swollen axons in the subcortical white matter was reported a postmortem adult case with prolonged partial SE lasting for 1 month [2]. Although microglial activation in the cortex of a 2-year-old AESD case was reported, specimen from the corresponding reduced diffusion region was not obtained [3]. Further extensive histological study is needed to elucidate the pathomechanism involved in the reduced subcortical diffusion seen in prolong SE and AESD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consents All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Takanashi J, Oba H, Barkovich AJ, Tada H, Tanabe Y, Yamanouchi H, Fujimoto S, Kato M, Kawatani M, Sudo A, Ozawa H, Okanishi T, Ishitobi M, Maegaki Y, Koyasu Y (2006) Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 66:1304–1309
2. Miki Y, Tanji K, Mori F et al (2017) Status epilepticus causing extensive microvascular change with astrocytosis and diffusion MRI abnormalities in the subcortical white matter. J Neurol Sci 382:55–57
3. Fujita Y, Takanashi J, Takei H, Ota S, Fujii K, Sakuma H, Hayashi M (2016) Activated microglia in acute encephalaopahty with biphasic seizures and late reduced diffusion. J Neurol Sci 366:91–93

4. Morioka T, Nishio S, Ishibashi H, Muraishi M, Hisada K, Shigeto H, Yamamoto T, Fukui M (1999) Intrinsic epileptogenicity of focal cortical dysplasia as revealed by magnetoencephalography and electrocorticography. Epilepsy Res 33:177–187
5. Shimogawa T, Morioka T, Sayama T, Haga S, Kanazawa Y, Murao K, Arakawa S, Sakata A, Iihara K (2017) The initial use of arterial spin labeling perfusion and diffusion-weighted magnetic resonance images in the diagnosis of nonconvulsive partial status epilepticus. Epilepsy Res 129:162–173
6. Matute C (2011) Glutamate and ATP signalling in white matter pathology. J Anat 219:53–64
7. Trendelenburg G, Dirnagl U (2005) Neuroprotective role of astrocytes in cerebral ischemia: focus on ischemic preconditioning. Glia 51:307–320