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Case report

Subventricular glial nodules in neurofibromatosis 1 with craniofacial dysmorphism and occipital meningoencephalocele

Tadanori Hamano[a,b,c,*], Tatsuro Mutoh[a,d], Hironobu Naiki[e], Norimichi Shirafuji[a,b], Masamichi Ikawa[a], Osamu Yamamura[a], Dennis W. Dickson[f], Shichiryoemon Aiki[g], Masaru Kuriyama[a,h], Yasunari Nakamoto[a]

[a] Second Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
[b] Department of Aging and Dementia (DAD), Faculty of Medical Sciences, University of Fukui, Fukui, Japan
[c] Life Science Innovation Center, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
[d] Department of Neurology, Fujita Health University, Toyoake, Japan
[e] Department of Pathological Sciences, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
[f] Department of Neuropathology, Mayo Clinic College of Medicine, FL, USA
[g] Department of Internal Medicine, Aiki Hospital, Echizen-city, Japan
[h] Department of Neurology, Ota Memorial Hospital, Fukuyama, Japan

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ABSTRACT

Background: Neurofibromatosis 1 (NF1) is autosomally inherited disorder, characterized by café au lait spots and multiple neurofibromas. Subventricular glial nodules (SVGN) are multiple gliosis bulging into the ventricular lumen, and histologically consist of astrocytes and their processes. Damage to ependymal cells induces SVGN formation.

Case report: This case report describes a 50-year-old man with NF1, craniofacial dysmorphism, including sphenoid dysplasia, bone defects at the middle posterior fossa, with disconnection of the parieto-occipital sutures, and the left orbital bone, and occipital meningoencephalocele. He died of status epileptics. Pathologically, many SVGN were found around the ventricular wall. Many ependymal cells were stripped during ventricular dilatation. Therefore, to prevent brain tissue insult from direct exposure to CSF, the proliferation of astrocytes and their processes was speculated to have substitute for ependymal cells and induced SVGN formation.

1. Introduction

Neurofibromatosis 1 (NF1) is an autosomally inherited disorder and the NF1 gene is located on chromosome 17q11.2, which codes for a tumor suppressor protein, neurofibromin. NF1 is characterized by café au lait spots and multiple neurofibromas. NF1 complicates many types of tumors, including optic glioma, and astrocytoma. Headache, hydrocephalus, and epileptic attack are common [1]. Craniofacial dysplasia, including sphenoid dysplasia [2], bone defects, and meningoencephalocele can also be observed in NF1 patients [3,4]. Subventricular glial nodules (SVGN) are multiple gliosis bulging into the ventricular lumen, and histologically consist of astrocytes and astrocytic processes [5]. Damage to ependymal cells induces the formation of SVGN [5]. We report a patient with NF1 and craniofacial dysplasia, who had occipital meningoencephalocele complicated by many SVGN.

2. Case description

A 50-year-old man was admitted because of generalized convulsions. His developmental milestones were normal. After graduation from junior high school, he worked at a laundromat, and had 2 daughters with no apparent skin lesions. He was able to walk by himself just before convulsing. On admission, he was 168 cm in height and had a blood pressure of 140/90 mmHg. He had multiple skin tumors with typical features of neurofibromas, and café au lait spots on his back, chest, abdomen, and upper extremities, which increased in number and size around age 40. He had a skull defect in the occipital area that was covered only by skin based, as demonstrated by skull X-ray (Fig. 1A); the defect was detected at birth. Ocular movement of the right eye was normal, but the left eye was fixed. The left eye protruded when the skull defect was pressed. There was hyperreflexia in both the upper and

* Corresponding author at: Second Department of Internal Medicine, Division of Neurology, Faculty of Medical Sciences, University of Fukui, 23-3 Matsuokashimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui 910-1193, Japan.
E-mail address: hamano@u-fukui.ac.jp (T. Hamano).

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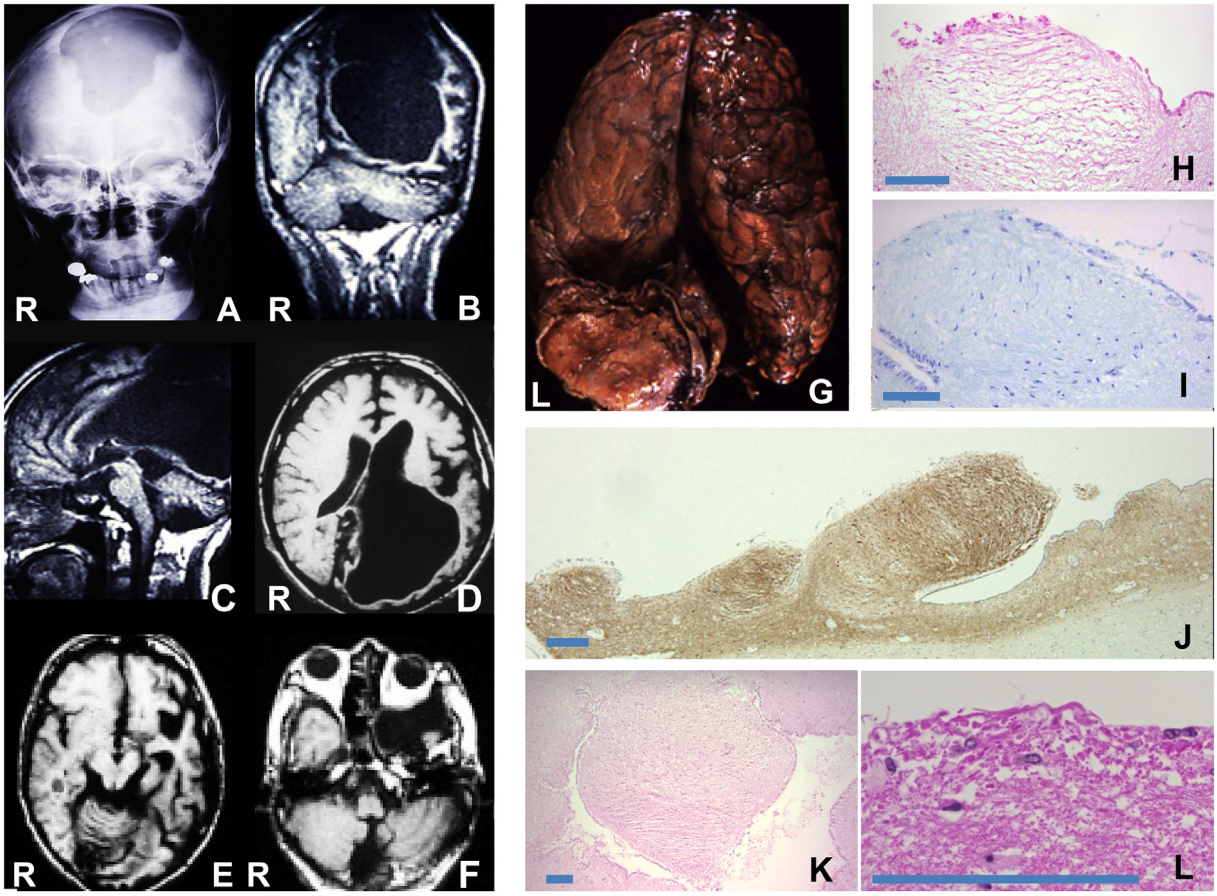

Fig. 1. (A) A large skull defect was observed on skull X-ray. (B) T1-weighted MRI finding in the brain (1.0 Tesla, Shimazu, TR/TE: 180/25): coronal imaging (B) and saggital imaging (C). Meningoencephalocele was observed at the left parietal lobe. Marked enlargement of the left posterior horn of the lateral ventricle, and thinning of the cortex were noted (D). There was atrophy at the left frontal lobe and left temporal lobe (E). Left sphenoidal dysplasia and arachnoid cyst in the cerebellum were also found (F). Macroscopically, the brain had large meningoencepholocele at the left parieto-occipital lobe (G). Marked whitish thickening of the arachnoid membrane was also noted. Microscopically, there was a series of SVGN bulging into the ventricular lumen at the right thalamus (H: hematoxylin and eosin (HE), I: Luxol Fast Blue (LFB) stain), right caudate nucleus (J: GFAP), and cerebral aqueduct (K). SVGN were positive on GFAP staining (J). Flattened or torn ependyma (LFB) over the subventricular glial nodule at the hippocampus was found (H, I). Normal ependyma was hardly found at the forth ventricle of the medulla (HE) (L). Scale Bar: 100 μm. R; right, L; left. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lower limbs, with right Babinski signs and right Chaddock sign. Generalized convulsions were controlled by repeated intramuscular infusion of diazepam 30 min after the presentation. He became conscious and responded correctly to simple commands. However, he was unable to speak and had severe left hemiplegia, including the face. Routine laboratory examinations revealed marked leukocytosis (WBC 20,900/mm^3) and mild renal dysfunction (creatinine; 2.0 mg/dl). EEG was not performed because he declined the examination.

T1-weighted MRI (1.0 Tesla, Shimazu, TR/TE: 180/25) demonstrated marked enlargement of the left posterior horn of the lateral ventricle and a thin cortex with meningoencephalocele (Fig. 1 B, C). There was left temporal lobe and frontal lobe atrophy (Fig. 1D). An arachnoidal cyst in the cerebellum (Fig. 1 B, C, E, F) and left sphenoidal dysplasia were also observed (Fig. 1F).

In the morning of the 6th hospital day, he slipped from the bed, and sustained head trauma. Convulsion recurred and were intractable despite anticonvulsant therapy. He died due to status epilepticus.

According to neuropathological findings, there were skull defects at the middle posterior fossa with disconnection of the parieto-occipital sutures, and at left orbital bone (Fig. 1A). Sphenoid dysplasia was also noted (Fig. 1F). Large meningoencephalocele was present at the left parieto-occipital lobe (Fig. 1G). The occipital pole of the left lateral ventricle was enlarged. Macroscopic findings showed that by the synaptophysin staining (Dako, Denmark), the cortical layer was discontinued at the occipital meningoencephalocele (Supplementary Fig. A). Instead of no staining by synaptophysin, glial fibrillary acidic protein (GFAP) (Sigma, St. Louis, MO, USA) staining was observed at the occipital meningoencephalocele (Supple Fig. 1B). This suggested marked gliosis after the disappearance of neurons at the occipital meningoencephalocele. Microscopic findings revealed that many SVGN were found below ependymal cells at the third ventricle (thalamus (Fig. 1H, I)), bilateral lateral ventricle (caudate nucleus (Fig. 1J)), cerebral aqueduct (Fig. 1K), and fourth ventricle. In some SVGN, flattened ependymal cells (Fig. 1H, I) were observed, and inflammatory cells had infiltrated some nodules (Fig. 1H-K). In the posterior horn of the bilateral lateral ventricles, diffuse subventricular gliosis was found and normal ependymal cells were rare (Fig. 1L). SVGN were positively stained by antibodies against GFAP (Fig. 1J), vimentin, and fibronectin. There was a fresh subdural hematoma in the right parieto-occipital lobe. Marked whitish thickening of an arachnoid membrane in the left hemisphere was also noted. In the gray matter of the left occipital lobe, numerous amyloid bodies were observed.

He was diagnosed with NF1 based strictly on the clinical and morphological features, including many café au lait spots, neurofibromas, sphenoid dysplasia, not accompanying acoustic neurinomas without genetic examination.

3. Discussion

This patient exhibited craniofacial dysmorphism with NF1. NF1 is a neurocristopathy and one of the classical disorders of the neural crest [6–8]. It was known that > 90% of craniofacial development originates from the neural crest, mainly from the mesencephalic neural crest that migrates rostrally from the embryonic dorsal midbrain to form the face and membranous bone of the calvarium (cranial vault) [9]. The malformations observed in this patient may have been caused by disturbances of neural crest formation or migration secondary to faulty genetic programming due to the NF1 mutation. Actually, our patient was complicated by large occipital meningoencephalocele (Fig. 1B, C, F, Supple Fig. 1) [3,4]. Cranial meningoencephalocele may occur due to mesodermal dysplasia and CSF pulsation will gradually enlarge the sac [3].

This patient had many SVGN bulging into the ventricular lumen, which histologically consisted of astrocytes and their processes not containing neurons [5]. Ventriculomegaly, especially due to obstructive hydrocephalus, causes stretching of the ependymal lining cells resulting in tearing and gaps or discontinuity in the ependymal, as observed in this patient (Fig. 1H, I, J, L). These gaps are filled by proliferated astrocytes and their processes to substitute for ependyma to prevent brain tissue insults from direct exposure to the CSF. The remaining ependymal cells are flattened because of the increased intraventricular pressure [5]. The mechanisms of SVGN formation in Larsen-like syndrome showing chronic persistent ventricular dilatation should be similar [10]. In this process the role of growth factors or cytokines are proposed [9].

To our knowledge, the complication of SVGN and NF1 has not been reported previously. SVGN were previously reported in patients presenting chronic inflammation of the central nervous system, including those with human immunodeficiency virus [11], neurocysticercosis [12], multiple sclerosis [13], tuberculous meningitis [14], post encephalitic Parkinsonism, and in mumps virus infected hamsters [15].

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2019.100213.

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Declaration of Competing Interest

None.

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