Neurological Complications Involving the Central Nervous System in Neurofibromatosis Type 1

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Abstract-

Objective: To investigate the neurological complications and characteristics of intracranial lesions in patients with neurofibromatosis type 1 (NF1) in Taiwan.

Background: Neurofibromtosis type 1 is a common autosomal dominant disorder characterized by cafe au lait spots, peripheral neurofibromas, Lisch nodules, and axillary freckling. Intracranial lesions such as optic gliomas and neurofibromatosis bright objects (NBOs) are common.

Methods: Patients with the diagnosis of NF1 based on criteria from the National Institutes of Health Consensus Conference (1988) between Jan. 1, 1983 and Oct. 30, 2005 were retrospectively evaluated at the Chung-Gung Memorial Hospital (CGMH). Case histories were analyzed for neurological complications of epilepsy, stroke, and pituitary as well as other intracranial lesions. Magnetic resonance imaging (MRI) examinations were also focused on the number, distribution, and change of NBOs as well as intracranial pathology including optic pathway or brain gliomas.

Results: The study population included 69 patients (28 females and 41 males) mean 25.1±15.0 years. Brain MRIs for 24 patients identified 1 meningioma, 1 optic glioma, and 4 other intracranial gliomas. In total, 14 patients had 52 NBOs. The most common anatomical sites for the NBOs were the globus pallidus and thalamus (15.4%), followed by the cerebellum and subcortical white matter (11.5%). The most commoly identified neurological complications were epilepsy (8.7%) and cerebral infarction (7.2%). These complications, however, were not correlated with intracranial lesions.

Conclusions: Neurofibromatosis bright objects are frequent neuroimaging findings in patients with NF1, and are at high risk of transforming into tumors. The incidences of epilepsy and young-onset cerebral infarction in NF1 patients in this study are higher than those in the general population. Neuroimaging studies are thus essential for NF1 patients to determine the extent of neurological complications; although the imaging findings may not be completely correlated with the clinical manifestations.

Key Words: Neurofibromatosis type 1, NF1, Neurofibromatosis bright objects (NBO), Epilepsy, Cerebral infarction, Optic glioma

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INTRODUCTION

Two distinct types of neurofibromatosis exist: neurofibromatosis type 1 (NF1), and neurofibromatosis type 2 (NF2). NF1 is a common autosomal dominant disorder in humans with an incidence of 1 in 2500-3300[1]. NF1 is characterized by the presence of cafe au lait spots, peripheral neurofibromas, Lisch nodules, axillary freckling, and skeletal dysplasia.

In addition to the major presentation of subcutaneous neurofibromas, NF1 may be complicated with several nervous system diseases. Neurological complications found in 138 patients were headache, hydrocephalus, epilepsy, lacunar infarction, white matter disease, intraspinal neurofibroma, facial palsy, radiculopathy, peripheral nerve sheath tumors, and polyneuropathy[1]. Intracranial lesions such as optic pathway tumors, meningiomas, and cerebral gliomas were also noted.

"Neurofibromatosis bright objects (NBO)" and "unidentified bright objects (UBO)" are common in patients with NF1[2-4], and are usually located in the globus pallidus, thalamus, hippocampus, and brain stem. Although most of these lesions would remain stable or even disappear over several years, some may undergo cancerous transformation into brain gliomas[5,6].

This study analyzed the clinical and MRI features of 69 NF1 patients admitted to Chang-Gung Memorial Hospital (CGMH) between Jan. 1983 and Oct. 2005. We described the distribution of neurological complications such as epilepsy and cerebral infarction, and MRI findings such as NBOs and tumors in these NF1 patients.

SUBJECTS AND METHODS

We retrospectively searched all CGMH admission charts with the diagnosis of "neurofibromatosis type 1" or "NF1" from Jan. 1983 to Oct. 2005. In addition to the Department of Neurology, the patients were also from the Departments of Plastic and Reconstructive Surgery, Dermatology, Orthopedics, and Pediatrics. Each patient was confirmed by National Institutes of Health Consensus Conference criteria[7]. Clinical features were reviewed by two authors (HY Hsieh and Tony Wu) to confirm NF1 diagnosis and to verify neurological complications.

The computed tomography (CT) and MRIs of these patients were evaluated by two experienced neuroradiologists (CJ Wang, and SC Chin). The neurological complications were focused in the CNS, and classified according to the presence or absence of tumors and NBOs. NBOs have been used to describe lesions in the white matter and gray matter with MRI characteristics of T1-hypointense or -isointense (some radiologists even describe the T1-signal as variable), and T2-hyperintense lesions without mass effect. Special attention was paid to the number, distribution, and change of NBOs, and also to the other intracranial pathology such as the optic pathway or brain gliomas and pituitary tumors. The clinical histories and imaging findings were further classified for the patients with epilepsy and stroke, two important neurological disorders. The age at diagnosis and characteristic features of the neurological complications were also recorded.

RESULTS

This series comprised 69 patients (28 females (40.6%) and 41 males (59.4%)). Thirty patients were ≥18 years and 39 were < 18 years. The mean age at diagnosis was 25.1±15.0 years (ranged 1~75 years). They came from several departments, including 5 born in our hospital, and 22 diagnosed by neurologists. The initial symptoms in these patients were variable. Most common presentations in their first visits were subcutaneous mass in the facial-cranial area, scalp, neck, trunk, buttock or limbs in 20 patients, followed by spinal deformities such as kypho-scoliosis in 9, convulsion in 7, and growth hormone deficiency in 2. Some patients were incidentally found to have characteristics of NF1 at admission because of systemic infection, metabolic diseases, autoimmune diseases, or other neoplasms.

In total, 28 patients underwent brain imaging: CT, 4; MRI, 24 (with magnetic resonance angiography (MRA) in 1 patient). Most of the images were arranged by neurologists, but may also be arranged by the other physicians when the patients had related symptoms. Brain CTs

showed multiple infarctions in 2 patients, and normal in the other 2. The MRA of a patient with left-middle cerebral artery infarction showed no obvious congenital vascular malformation.

Review of all brain MRIs, 20 (83.3%) were abnormal. Among them, 1 had cortical atrophy of the right hemisphere, 1 had diffuse encephalomalacia, and 1 had a suspected hemangioma in the skull base. These 3 patients were not analyzed in our study. Seventeen NF1 (70.8%) patients had tumors and NBOs, including 1 of optic glioma, 1 of meningioma, 4 of brain gliomas, and 2 of pituitary tumors. Additionally, 14 patients had ≥ 1 NBOs (Table 1). In total, 52 NBOs were demonstrated by MRIs in 14 patients (58.3%). Distributions of NBOs and ages were compared with that in a series by Griffiths et al.[5] (Table 2). 11 patients had at least two NBOs, and 3 had single NBO. These lesions were located in the midbrain, pons, and left mesial temporal areas. There were 5 patients who had both NBOs and intracranial tumors.

DISCUSSION

The NF1 was previously considered to be a disease with chiefly peripheral manifestations, such as cafe au lait spots, peripheral neurofibromas, Lisch nodules, and axillary freckling. Diagnosis of NF1 is typically made during childhood based on physical findings and a positive family history in about 50% of cases. Today further understanding of the disease indicates that in addition to peripheral lesions such as a subcutaneous mass or neurofibroma, many CNS lesions were often found in NF1 patients[1]. Moreover, NF1 patients have a higher tumor incidence (CNS or PNS) than the general population. Incidence of abnormalities in brain MRIs of our patients was as high as 83.3%. At least one brain imaging study is mandatory for each NF1 patient to screen possible CNS lesions, even if the patient has no symptoms and signs of CNS involvement.

The most frequent NF1 complication of the central nervous system is optic glioma that occurs in 5~15% of patients, and may usually require follow-up neuroimaging examinations[8-11]. A study that analyzed 127 intracranial tumors in NF1 patients indicated that 84 (66%) were optic pathway tumors (OPT), with visual loss (58%) and precocious puberty (10%) being the two most common symptoms[9]. Interestingly, only one optic glioma was identified in our patients. This may be partly ascribable that some patients without neurological deficits do not have brain imaging examination in this study. Also, different groups of age and source may be responsible for the lower incidence of optic gliomas[8-10]. One more notable finding is that 3 subjects aged < 18 years had

Table 1. *Neurological complications involving the central nervous system and MRI findings in the patients with neurofibromatosis type 1*

MRI findings (n=24)	Numbers (%)
Brain tumors	8 (33.3)
Optic glioma	1 (4.2)
Meningioma	1 (4.2)
Pituitary adenoma	2 (8.3)
Brain glioma	4 (16.7)
NBOs	14 (58.3)
Neurological complications (n=69)	**Numbers (%)**
Epilepsy	6 (8.7)
Cerebral infarction	5 (7.2)

MRI: magnetic resonance imaging; NBOs: neurofibromatosis bright objects.

Table 2. *Distribution of NBOs in neurofibromatosis type 1*

	Griffiths, 1999[6]	Our series, 2005		
Ages (years old)	≤ 16	5 ~ 65	< 18	≥ 18
Total numbers of NBOs (patient numbers)	205 (43)	52 (14)	38 (10)	14 (4)
Location of NBOs	Number of NBOs (%)			
Globus pallidus	62 (30.4)	8 (15.4)	8	0
Thalamus	22 (10.8)	8 (15.4)	8	0
Cerebellum	48 (23.5)	6 (11.5)	4	2
Subcortical white matter	-	6 (11.5)	3	3
Hippocampus and amygdala	22 (10.3)	6 (11.5)	4	2
Midbrain	33 (16.2)	5 (9.6)	4	1
Cortex	-	5 (9.6)	0	5
Putamen	1 (0.5)	3 (5.8)	3	0
Pons	9 (4.4)	3 (5.8)	3	0
Medulla	7 (3.4)	2 (3.8)	1	1
Internal capsule	1 (0.5)	0	0	0

NBOs: neurofibromatosis bright objects.

growth hormone deficiency or panhypopituitism, and 2 had pituitary adenoma. We therefore suggest that endocrine disorders of CNS, such as growth hormone deficiency and precocious puberty, should be carefully checked for all NF1 subjects aged < 18 years[9].

The nature and significance of NBOs is still unclear; however, NBOs usually show hyperintense signals in T2-weighted images, and hypointense or occasionally isointense signals in T1-weighted images (Fig.). Typically, NBOs may remain stationary, or regress slowly, or even spontaneously disappear without any treatment. On the other hand, they may also be transformed into tumors[6,12,13]. The NBOs with marked enhancement (in T1-weighted images), mass effect, and increase in size would typically indicate a tendency toward tumor transformation[5,6,14]. Griffiths et al. described 8 cases with brain tumors, 6 of which seemed to have developed after the follow-up imaging study. Five tumors were transformed from NBOs, and 1 tumor that was not overlapped in position with a previous NBO developed in the splenium of the corpus callosum[5]. In our study, 4 patients had brain tumors or enhanced brain lesions. One tumor in the cerebellum and one in the fronto-parietal area were low-grade astrocytomas. However, no MRIs were available to support the evolution of NBOs into tumors. Three patients had enhanced lesions in the insular cortex, brain stem, and corpus callosum. The patient with an enhanced insular lesion (and a diagnosis of probable tumor) received radiotherapy and has remained stable for 3 years thereafter, with the latest MRI study showing decreased size of the lesion. The patient with an enhanced lesion in the brain stem did not receive radiotherapy and died several years later. The patient with NBOs in the thalamus, cerebellum and corpus callosum had blurred vision, which was her only neurological symptom. However, the latest neuroimaging study showed that the corpus callosum lesion had become enhanced. Regular imaging follow-up for this patient is important due to this newly enhanced NBO.

The overall frequency of NBOs is 43~77% in NF1[14,15]. In children with NF1, 93% of patients have NBOs, which was a common finding through the age of 4-10 years[5]. Previous studies showed that NBOs are most frequently identified in children and rarely found in those >20 years of age (93% of NBOs were found in patients <15 years)[5,15]. The most common sites of NBOs in previous studies were the globus pallidus (30.4%), followed by the cerebellum (23.5%) and midbrain (16.2%). In our series, the most common sites of NBOs were the globus pallidus and thalamus (15.4%), followed

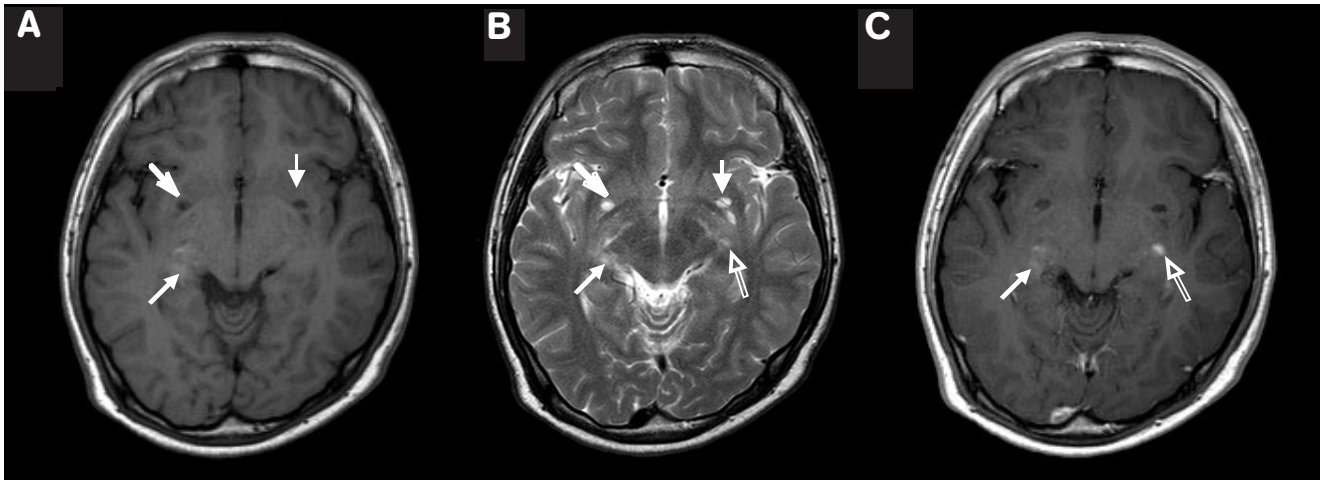

Figure. (A) The MRI study of a 15-year-old boy revealed 3 NBOs with hyper- or hypo-intensity on T1-weighted images (arrows) in the thalamus and putamen on both sides. (B) Four hyperintense lesions were observed on T2-weighted images (arrows). (C) One small NBO was only minimally enhanced (arrow), whereas another NBO was markedly enhancement (empty arrow) after contrast injection on T1-weighted images.

by the cerebellum and subcortical white matter (11.5%) (Table 2). In this regard, it is interesting to note that only few NBOs in subcortical white matter and cortex were reported before. In our study, 5 NBOs in the cortex were all found in patients aged ≥ 18 years, and this group also included half of the NBOs located in subcortical white matter. This is consistent with the findings of Itoh et al, where most of NBOs in cortex or subcortical white matter were found in adulthood[15]. More serial imaging studies are necessary to evaluate if the cortical or subcortical NBOs indeed develop after adulthood. It is also found that in our patients with multiple cortical NBOs, 1 had a residual cortical astrocytoma, and 1 had a cerebellar glioma before. Although series of neuroimaging data are not available at this point, we propose patients with cortical NBOs should be monitored more closely than those with NBOs in the other locations because of the probability of higher risk of transforming into gliomas. We would also reemphasize that NBOs should be monitor regularly, especially when they are identified in childhood[5]. A recent report suggested that magnetic resonance spectroscopy (MRS) may be helpful in the differentiation between groups of tumors/atypical NBOs and typical NBOs[16].

Roughly 4.2~6% of NF1 patients have epileptic seizures, a prevalence rate approximately twice that in the general population[17-19]. Complex partial seizure is the major seizure pattern in such patients, and seizure onset ranges from 4 days to > 20 years. In our series, 6 patients (8.7%) had epileptic seizures and took antiepileptic medications, and the ages of these patients were 1~51 years. One patient had both generalized tonic-clonic seizure (GTCS) and simple partial seizure (SPS). 1 had GTCS and 1 had simple partial seizure (SPS) only. In addition, 2 patients had non-convulsive seizures, and 1 had infantile spasms. The EEG showed epileptiform discharges in 4 patients, diffuse slow waves in 1 patient, and normal findings in the other one. Among them, 2 patients had NBOs or tumors, 1 had diffuse encephalomalacia, and 1 had multiple infarctions. The EEG findings indicated left fronto-parietal discharges in 1 patient with multiple NBOs (with one located in the left frontal area) and a right fronto-parietal tumor. The seizure patterns of this patient included both GTCS and SPS (right arm shaking without loss of consciousness). We suspected that the epileptogenic foci may be related to the cortical NBOs. However, except for 1 patient, the EEG findings were in general not well correlated with the results of neuroimageing studies. Although our study showed that the likelihood of significant clinical findings is low, and most patients with brain lesions did not have seizures, a neuroimaging study is indicated for any NF1 patients with seizures to exclude organic lesions.

Patients of NF1 had an increased incidence of cerebral vasculopathy in the anterior cerebral circulation, and less commonly in the posterior cerebral circulation[20,21]. In previous studies, most arterial anomalies were incidental findings during imaging studies, and no associated intracranial hemorrhage was reported. Cerebral infarction was reported in 2 NF1 children with MoyaMoya vessels, and 1 patient had lacunar infarction at 19 years of age[1,20]. The thalamic infarction in one MoyaMoya patient was subclinical and the other 2 patients presented with acute hemiparesis.

In our study, four patients had multiple lacunar infarcts, and 1 patient had a large infarction in the territory of the left middle cerebral artery. The mean age of these patients was 46.4±8.7 years (ranged 35~59 years). No intracranial hemorrhage or vascular anomalies were observed. Although some of the patients had the other risk factors such as hypertension or diabetes, the young age of onset and increased incidence of stroke may be consistent with the known vasculopathy.

CONCLUSION

Patients with neurofibromatosis type 1 had a higher likelihood for intracranial neoplasm than the general population. Therefore, a series of brain imaging examination is recommended for any patient with diagnosis of NF1, especially those with enhanced or cortical NBOs. Additionally, children with numerous NBOs or enhanced NBOs should receive close follow-up examinations. An individualized therapeutic plan must be developed for each patient, based on the extent of transformation revealed by the serial neuroimaging studies.

In our study, the incidence of epilepsy and cerebral infarction in NF1 patients are higher than that in the general population. However, their NBOs were not correlated with epilepsy. Although no special vascular malformations or peculiar areas of infarction were found, our stroke patients in general had a young age. Consequently, imaging studies should be applied for all NF1 patients to rule out any intracranial lesions and vascular anomalies, even though the neuroimaging findings may not be well correlated with the clinical presentations.

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