

Case Report

Neurofibromatosis Type I Associated Multiple Sclerosis[†]

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Neurofibromatosis (NF) type I is a common autosomal dominant disease that principally affects the skin and peripheral nervous system. Neurofibromatosis type I associated multiple sclerosis is a very rare condition. A 28-year old NF1 man developed progressive spastic-ataxic gait, left side dysmetria, right internuclear ophthalmoplegia, spastic dysarthria. MRI of the brain depicted Dawson finger appearance demyelination of the corpus callosum and other multifoci demyelinating lesions typical for MS. CSF revealed high CSF protein with negative oligoclonal band. Visual evoked potential showed prolonged P100 latency, abnormal wave form and temporal dispersion bilaterally. The syndrome partially responded and stabilized with corticosteroid. Six months later, progression of the syndrome characterized by paraparesis, bilateral cerebellar hemispheric syndrome and bilateral internuclear ophthalmoplegia occurred. Repeated MRI revealed more extensive white matter lesions extended into centrum semiovale. The progressive syndrome did not respond to corticosteroid. Primary progressive multiple sclerosis was diagnosed. Only thirteen cases with NF1 and multiple sclerosis have been described in the literature. The association has been hypothesized to be related to mutations in the neurofibromin protein or oligodendrocyte-myelin glycoprotein (OMgp) gene.

Keywords: Neurofibromatosis type I, Multiple sclerosis

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Neurofibromatosis type I (NF1) is a common and worldwide neurogenetic disease⁽¹⁾. Multiple sclerosis (MS) is also a common demyelinating disease in Western countries⁽²⁾. However, MS especially in the form of primary progressive disease is very rare in Thailand⁽³⁾. Association of NF1 with MS has been rarely described in the literature⁽⁴⁻¹¹⁾. The most common form of MS associated with neurofibromatosis is primary progressive MS⁽⁷⁾. Advances in neurogenetics will provide important insight for theoretical link between these two entities. Here, the authors report the first reported case of NF1 associated with MS in Thailand and this will provide the information for association between these two diseases in Asian populations.

Case Report

A 28 year-old man was diagnosed with NF1 when he was 24 years old on the basis of multiple more than 15 mm in diameter of cafe-au-lait lesions,

multiple cutaneous neurofibroma and bilateral Lisch nodules. He had no family history of NF1. One and a half years ago he developed progressive spastic paraparesis, ataxic gait with a tendency to fall to the left. He could not walk without assistance. He also developed spastic dysarthria without dysphagia and double vision. Cranial nerve examination revealed right internuclear ophthalmoplegia (INO). Other cranial nerves including optic nerves were unremarkable. Motor examination revealed spastic paraparesis grade IV/V in both legs. Hyperreflexia in all extremities and bilateral positive Babinski's sign were detected. Impaired left side finger to nose test and positive tandem's walk with a tendency to fall to the left side were observed. MRI of the brain revealed hypersignal intensity lesion in T2-weight imaging in the pattern of Dawson finger appearance at corpus callosum bilaterally and at right medial side of midbrain (Fig. 1A & B). MRI of the spinal cord revealed increased signal intensity lesion in T2-weight imaging at cervical cord C1-2 level and thoracic cord T4 level (Fig. 2). These hyperintensity lesions were not enhanced after gadolinium injection. Cerebrospinal fluid (CSF) examination revealed normal pressure, colorless, acellular CSF with protein of 115 mg/dl,

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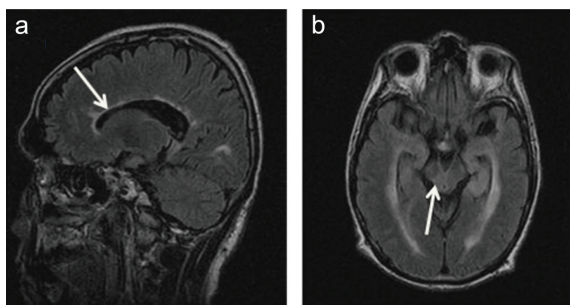


Fig. 1 MRI Flair image showed a) increased signal intensity at periventricular and corpus callosum bilaterally b) increased signal intensity at right midbrain

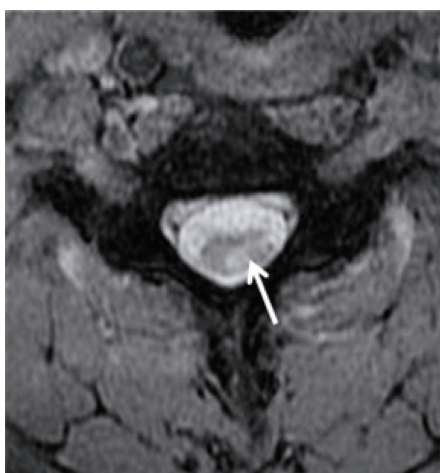


Fig. 2 MRI C-spine showed increased signal intensity in the spinal cord

sugar of 52 mg/dl and negative for oligoclonal band. Visual evoked potentials showed prolonged P100 latency, abnormal wave form and temporal dispersion bilaterally compatible with optic neuropathy. He received methylprednisolone 1 g for 3 days with a maintenance dose of prednisolone 60 mg/day. The steroid was tapered within 1 week. After the treatment, the clinical profiles were mildly improved and he could walk with a spastic gait. Double vision and internuclear ophthalmoplegia were not improved. Six months prior to this admission, spastic paraparesis and ataxic gait became worse and he could not ambulate. The double vision was also worsening. Physical examination revealed spastic paraparesis with ataxic gait, impaired finger to nose and heel to knee both sides, bilateral INO, spastic dysarthria. MRI of the brain revealed

increasing in non-enhanced high signal intensity lesions in T2-weight image along corpus callosum, bilateral periventricular white matter. The midbrain lesion was not changed from the previous study. CSF examination revealed normal pressure, acellular CSF with protein of 107 mg/dl, sugar of 54 mg/dl and negative oligoclonal bands. Primary progressive MS was diagnosed. A course of intravenous methylprednisolone and oral prednisolone was given without any improvement.

Discussion

In the present case, NF1 was diagnosed according to National Institutes of Health Consensus Development Conference diagnostic criteria for NF1⁽¹²⁾. The patient also fulfilled McDonald criteria revision 2005⁽¹³⁾ for the diagnosis of primary progressive MS *i.e.* 1) progression of clinical features more than 1 year 2) MRI showed multiple increase signal intensity in T2-weight images more than four lesions in brain and evidence of demyelination of both optic pathway documented by visual evoked potential 3) MRI of spinal cord showed 2 high signal intensity lesions in T2-weight images.

The association of MS with NF1 is a very rare and only 13 case reports have been documented in the literature⁽⁴⁻¹¹⁾. 3/13 cases were in non-English literatures and were not included in the discussion. Ten cases in English literatures including the presented cases are summarized in Table 1. Interestingly NF1 who developed MS usually had MS in the form of primary progressive subtype (8/11 cases, 72%) and this form is not a common subtype of MS occurring only 10-15% in MS populations⁽¹⁴⁾. Mean age of onset in primary progressive MS associated NF1 was 35.25 years but typically mean age of onset in primary progressive MS was 40 years⁽¹⁴⁾ while mean age of onset in relapsing remitting MS was 30 years⁽¹⁴⁾. Classically clinical presentation in the primary progressive MS is spinal cord syndrome⁽¹⁴⁾. Five of seven patients (71%) of primary progressive MS associated NF1 presented without spinal cord syndromes. Six of nine patients (66%) had *de novo* mutation of NF1 gene. Usually new mutations occur in about half of NF1 populations⁽¹⁵⁾. The associations of NF1 and primary progressive MS with these unusual patterns may indicate that the association might not be coincidental. Oligoclonal bands in CSF were usually positive in primary progressive MS with or without NF1⁽¹⁴⁾. The responsiveness to therapy in NF1 associated with primary progressive MS is poor and parallel with

Table 1. Summary of 11 cases of NF1 associated with MS

Age at onset	MS type & clinical	MRI findings	CSF OCB	Family Hx of NF1	Treatment	Response
Female ⁽⁴⁾ 42 yrs.	PP - Progressive painful tingling both hands and feet - Rt. hemiparesis showed enhancement	- Multiple area of increased SI in T2 in white matter of both cerebral hemisphere - Some of the lesions	+VE	+VE	Intravenous methyl prednisolone	Not improved
Female ⁽⁴⁾ 23 yrs.	PP - Optic atrophy - Vertical nystagmu - Bilateral INO - Left limb ataxia	Not done (CT showed several areas of low density in a periventricular areas)	+VE	+VE	No data	No data
Female ⁽⁴⁾ 26 yrs.	PP - Optic atrophy - Ataxic spastic paraparesis	- Multiple area of increased SI in T2 at periventricular and both cerebral hemispheres	+VE	-VE	Intravenous methyl prednisolone	Not improved
Female ⁽⁴⁾ 42 yrs.	PP - Tetraparesis with hyperreflexia and extensor plantar responses - Urinary urgency	- Multiple area of high signal lesions In T2 at white matter of both cerebral hemispheres, pons and cerebellar hemispheres - Multiple high signal lesions in lower part of the medulla down to upper cervical cord	N/A	-VE	No data	No data
Male ⁽⁴⁾ 44 yrs.	PP - Pale optic disc - Bilateral INO - Ataxic, spastic hemiparesis	- Increased SI in the white matter of both cerebral hemispheres in the centrum semiovale, pons, periventricular white matters, cerebral peduncles	N/A	-VE	Intravenous methyl prednisolone	Not improved
Male ⁽⁷⁾ 19 yrs.	RR - Diplopia, nystagmus on horizontal gaze - Bilateral plantar response - Mild distal hypoparesthesia	- Multiple areas of altered signal in the white matter of both cerebral hemispheres (corpus callosum, centrum semiovale, periventricular regions) - Some enhanced lesions	+VE	-VE	Intravenous methyl prednisolone	Improved
Female ⁽⁷⁾ 30 yrs.	SP - Bilateral glove-like paraesthesia - Painful tingling in the hands, legs, feet - Weakness and stiffness of the legs	- Multiple areas of altered signal in cerebral white matter and in cervical spinal cord	+VE	-VE	Intravenous methyl prednisolone	Improved
Male ⁽⁷⁾	PP					

PP = primary progressive; SP = secondary progressive; RR = relapsing remitting; N/A = not available; +VE = positive; -VE = negative; OCB = oligoclonal band; Hx = history; NF1 = neurofibromatosis type 1; MS = multiple sclerosis; INO = internuclear ophthalmoplegia; SI = signal intensity

Table 1. (cont.)

Age at onset	MS type & clinical	MRI findings	CSF OCB	Family Hx of NF1	Treatment	Response
46 yrs.	- Bilateral paraesthesia at the feet - Mild cerebellar tremor and ataxic in left arm	- Multiple lesions in both cerebral hemisphere, predominantly at periventricular white matter	+VE	+VE	Intravenous methyl prednisolone	Mild/transient benefit
35 yrs. ⁽⁵⁾ Female ⁽⁸⁾	PP SP	- Multiple lesions in MRI	N/A	N/A	N/A	N/A
28 yrs.	- Retrobulbar optic neuritis - Spastic paraparesis	- Multiple periventricular white matter lesions	+VE	N/A	Dexamethasone	Improved
Our case Male 24 yrs.	PP - Right INO-Spastic paraparesis - Ataxia both sides	- Multiple area of increased SI in T2 at periventricular white matter, corpus callosum bilaterally and right side of midbrain - Increased SI in T2 at C and T spine	-VE	-VE	Intravenous methyl prednisolone	Not improved

PP = primary progressive; SP = secondary progressive; RR = relapsing remitting; N/A = not available; +VE = positive; -VE = negative; OCB = oligoclonal band; Hx = history; NF1 = neurofibromatosis type 1; MS = multiple sclerosis; INO = internuclear ophthalmoplegia; SI = signal intensity

classical primary progressive MS without NF1⁽¹⁴⁾. The presented patient follow this pattern of association. However, oligoclonal bands was negative in the presented case. According to the clinical study in Thailand, MS in Thai populations had oligoclonal band positive in only 21%⁽³⁾.

The gene for the NF1 has been located on chromosome 17q11.2 which encodes neurofibromin⁽¹⁶⁾. Neurofibromin has function as a tumor suppressor and this protein reduced cell proliferation by inactivation product of proto-onco gene, p21 ras protein⁽¹⁷⁾. Another genetic derangement on chromosome 17q11.2 in NF1 is mutations of oligodendrocyte myelin glycoprotein (OMgp)⁽¹⁶⁾. OMgp is essential for myelination or survival of myelinated axon⁽⁶⁾. The etiologies of MS are not well understood but both genetic and environmental factors may play a role⁽¹⁸⁾. MHC and T-cell receptors association with MS had been documented as the genetic associations⁽¹⁹⁾. For linkage studies, the Transatlantic multiple sclerosis genetics cooperative showed highest evidences for linkage at chromosome 17q11⁽²⁰⁾.

There are two major genetics hypothesis for the association between NF1 and MS^(7,16). The first hypothesis focused on neurofibromin protein⁽⁷⁾.

Neurofibromin protein suppresses cellular proliferation by inactivated the proto-oncogene results in suppression of tumor formation⁽⁷⁾. In NF1 patient, lack of neurofibromin activity results in tumor formation or cell over-proliferation in many systems. Lack of suppressor function of neurofibromin may also effect the immune system and results in over-activity of the immune system⁽⁷⁾. MS is the immunological disease caused by dysregulation of immune system and may be related to NF1 via neurofibromin function. The second hypothesis proposed the relationship between oligodendrocyte myelin glycoprotein (OMgp) and MS⁽¹⁶⁾. In NF1 patient, the OMgp gene may not function normally and promote demyelination in susceptible MS patients⁽⁴⁾. However, this hypothesis has not been well accepted due to the study of oligodendrocyte myelin glycoprotein gene in four patients with NF1 and primary progressive MS and the present study documented mutation of OMgp gene only 2 from 4 patients⁽⁶⁾. Moreover, mutation in OMgp gene is also detected in a normal population and MS population in the same percentage⁽²¹⁾. Although there was no conclusive genetic linkage between NF1 and MS, recent and rapid advances in genetics may clarify the association between NF1 and MS in the future.

Potential conflicts of interest

None.

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โรค neurofibromatosis ชนิดที่ 1 พบร่วมกับโรค multiple sclerosis

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โรค neurofibromatosis ชนิดที่หนึ่งเป็นโรคที่พบบ่อยซึ่งถ่ายทอดแบบเด่นส่วนใหญ่มีผลต่อผิวหนัง และระบบประสาทส่วนปลายโรค neurofibromatosis ชนิดที่หนึ่งพบร่วมกับโรค multiple sclerosis เป็นภาวะที่พบได้ยากมาก ผู้ป่วยชายโรค neurofibromatosis ชนิดที่หนึ่งอายุ 28 ปี มีอาการเดินเซมากขึ้นเรื่อย ๆ กระยะด้านซ้ายพลาดตาขวาตกลงเข้าด้านในไม่ได้, พูดไม่ชัดแบบเกร็ง เอ็มอาร์ไอของสมองพบลักษณะนิ้วของ Dawson ที่บริเวณ corpus callosum และพบรอยโรค demyelination หลายตำแหน่งจำเพาะกับโรค multiple sclerosis การตรวจน้ำไขสันหลังพบโปรตีนสูงแต่ไม่พบแถบ oligoclonal visual evoked potential แสดงระยะเวลาเกิดพี 100 นาน, รูปร่างของคลื่นผิดปกติ และ temporal dispersion ทั้ง 2 ข้าง โรคตอบสนองบางส่วน และคงที่ด้วยคอร์ติโคสเตียรอยด์ 6 เดือนต่อมาโรคกำเริบมีลักษณะขาอ่อนแรง 2 ข้าง, กลุ่มอาการโรค cerebellar 2 ข้าง, และตา 2 ข้าง มองเข้าในไม่ได้ เอ็มอาร์ไอของสมองซ้ำพบรอยโรคในเนื้อสมองขาว กว้างขวางขึ้นขยายไปในส่วน centrum semiovale โรคที่มากขึ้นไม่ตอบสนองต่อคอร์ติโคสเตียรอยด์ โรค primary progressive multiple sclerosis ถูกวินิจฉัยมีเพียง 13 ราย ที่เป็น neurofibromatosis ชนิดที่หนึ่ง และ multiple sclerosis บรรยายในวรรณกรรม ความสัมพันธ์ถูกตั้งสมมุติฐานว่า เกี่ยวเนื่องกับการกลายพันธุ์ในโปรตีน neurofibromatosis หรือ จีน oligodendrocyte-myelin glycoprotein (OMgp)
