

## Clinical Characteristics of Epilepsy and Its Risk Factors in Neurofibromatosis Type 1: A Single-Center Study

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**Purpose:** This study investigated the clinical characteristics and risk factors of epilepsy in patients with neurofibromatosis type 1 (NF1) at a tertiary center.

**Methods:** The medical records of 103 children diagnosed with NF1 from February 2009 to July 2019 were retrospectively reviewed. Demographic features, NF1-related features, seizure characteristics, treatment outcomes, and electroencephalography and brain magnetic resonance imaging (MRI) findings were compared between patients with and without epilepsy.

**Results:** Among the 103 patients (median age, 11.5 years; age range, 1.0 to 34.8), 14 (13.6%) had epilepsy. The median age of seizure onset was 5.8 years (range, 1.1 to 18.9). Focal and generalized seizures were observed in nine (64.3%) and six (42.9%) patients, respectively. Five patients (35.7%) had a history of status epilepticus and one of them died of it. Two patients (14.3%) had drug-resistant epilepsy. On brain MRI obtained at the time of seizure onset, seven (50%) patients had unidentified bright objects and three (21.4%) had other structural abnormalities. Learning disability (odds ratio [OR], 4.5; 95% confidence interval [CI], 1.17 to 17.5) and a family history of epilepsy (OR, 39.7; 95% CI, 3.78 to 416.53), but not structural abnormalities, were significant risk factors for epilepsy.

**Conclusion:** Epilepsy was more common in NF1 patients than in the general population. NF1 patients with epilepsy had various seizure types, but exhibited relatively good outcomes. The types of brain abnormalities were not significantly different between patients with and without epilepsy. Our results suggest that mechanisms other than structural brain abnormalities should be considered epileptogenic in NF1 patients.

**Keywords:** Neurofibromatosis 1; Epilepsy; Learning disabilities; Risk factors

## Introduction

Neurofibromatosis type 1 (NF1) is one of the most common neurocutaneous disorders with a prevalence of approximately from 1/2,000 to 1/5,000 in most population-based studies [1]. It is an autosomal dominant genetic disorder caused by mutation of the

*NF1* gene, which encodes neurofibromin—tumor suppressor protein that inhibits intracellular Ras signaling [2]. Neurofibromin is highly expressed within the cerebral cortex during embryologic development and it may play an important role in neurodevelopment [3,4]. Hence, patients with NF1 present with not only typical characteristic signs of NF1 such as café au lait spots, Lisch nod-

ules, axillary or inguinal freckling, neurofibromas, distinctive osseous lesions, and optic gliomas, but also with neurologic symptoms, such as learning disability, behavioral problems, attention deficit, headache, and epilepsy.

The prevalence of epilepsy in patients with NF1 is reportedly 4% to 13%, higher than the general population (0.45% to 1%) [5-8]. Although this epilepsy predisposition was first postulated more than 30 years ago, the underlying mechanism has not been fully elucidated [9]. Several studies have described factors associated with epilepsy in NF1, but no consistent patterns have yet emerged [5,6,8,10-12]. This study aimed to analyze the clinical features and risk factors of epilepsy in patients with NF1 at a single tertiary center.

## Materials and Methods

We retrospectively reviewed the medical records of all patients diagnosed with NF1 at Kyungpook National University Hospital from February 2009 to July 2019. All patients fulfilled the National Institutes of Health diagnostic criteria for NF1 [13]. We collected the following data from the patients with epilepsy: age of seizure onset, seizure semiology and frequency, number of anti-epileptic drug (AED) medications, family history of epilepsy, and electroencephalography (EEG) findings. Patients who had not visited the hospital for the past year were interviewed via telephone for data collection. Epilepsy was defined and classified according to the International League Against Epilepsy classification [14-16]. Patients with febrile seizures were excluded. Drug-resistant epilepsy (DRE) was defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules to achieve sustained seizure freedom [17].

Clinical characteristics, including demographic features, family history, NF1-related features, learning disability, and brain magnetic resonance imaging (MRI) findings, were compared between patients with and without epilepsy to identify epilepsy risk factors. Learning disability was determined based on neuropsychiatric testing and parental interviews. Neuroimaging findings were reviewed by an experienced neuroradiologist blinded to patient information. Brain MRI findings closest to the time of seizure onset in patients with epilepsy were compared with the latest MRI findings in patients without epilepsy. This study was approved by the Institutional Review Board of the Kyungpook National University Hospital (IRB file no. 2020-06-050). Written informed consent by the patients was waived due to a retrospective nature of our study.

Demographic data are presented as proportions or medians. Clinical characteristics between the patients with and without epilepsy were analyzed using the two-tailed Fisher's exact test or chi-

square test for categorical variables and the Mann-Whitney U test for continuous variables. To identify epilepsy risk factors in NF1, multiple logistic regression model with a backward stepwise approach was used. Analysis results are presented using odds ratios (ORs) with 95% confidence interval (CI).  $P < 0.05$  was considered statistically significant.

## Results

### 1. Patient characteristics

The study included 103 patients (52 female, 51 male) for analysis. Median patient age was 11.5 years (range, 1.0 to 34.8). Median age at diagnosis and follow-up duration were 4.5 years (range, 0.1 to 20.5) and 73.0 months (0.5 to 282.4), respectively. Among them, 14 patients (13.6%, three females) had epilepsy. Median age at diagnosis and follow-up duration of the patients with epilepsy were 5.4 years (range, 0.4 to 11.0) and 76.8 months (range, 12.4 to 211.3), respectively. Seven patients (50%) had a family history of NF1, two of whom inherited it from their affected mothers. Nine patients (64.3%) had a learning disability. Five patients (35.7%) had a family history of epilepsy; two had affected siblings. Characteristic signs and symptoms of NF1 were present as follows: café au lait spots ( $n = 14$ ), axillary or inguinal freckling ( $n = 8$ ), neurofibromas ( $n = 3$ ), Lisch nodules ( $n = 7$ ), scoliosis ( $n = 2$ ), and skeletal dysplasia ( $n = 1$ ). MRI findings at seizure onset were normal in six patients (42.9%) and unidentified bright objects (UBOs) in seven (50%). Three patients showed structural abnormalities except UBOs, including moyamoya syndrome ( $n = 1$ ), subdural hematoma ( $n = 1$ ), and Chiari malformation type 1 ( $n = 1$ ). No brain tumor was observed. Table 1 shows the comparison of clinical characteristics between the patients with and without epilepsy. The epilepsy group had a significantly higher proportion of patients with learning disability ( $P = 0.005$ ) and family history of epilepsy ( $P < 0.001$ ). Structural brain abnormalities in MRI were not different between the two groups.

### 2. Epilepsy in neurofibromatosis type 1

Table 2 shows the epilepsy characteristics of the patients with epilepsy. In these 14 patients, median age of seizure onset was 5.8 years (range, 1.1 to 18.9). Nine (64.3%) had focal seizures (focal impaired awareness motor seizure,  $n = 4$ ; behavioral arrest,  $n = 2$ ; focal aware motor seizure,  $n = 2$ ; focal to bilateral tonic-clonic seizure,  $n = 3$ ), six (42.9%) had generalized seizures (absence seizure,  $n = 1$ ; generalized atonic seizure,  $n = 1$ ; generalized tonic seizure,  $n = 4$ ), and one had unknown seizure (epileptic spasm). Epilepsy type was classified as focal in seven patients, combined focal and generalized in two, generalized in four, and unknown in one. An

**Table 1.** Comparison of clinical characteristics between patients with and without epilepsy

Characteristic	Patients with epilepsy (n=14)	Patients without epilepsy (n=89)	P value
Male sex	11/14 (78.6)	40/97 (41.2)	0.023
Age at diagnosis (yr)	5.4 (0.42–11.0)	4.4 (0.05–20.5)	0.913
Follow-up duration (mo)	76.8 (12.4–211.3)	73.0 (0.5–282.4)	0.397
Family history of NF1	7/14 (50)	34/89 (38.2)	0.558
Family history of epilepsy	5/14 (35.7)	1/89 (1.1)	<0.001
Learning disability	9/14 (64.3)	22/89 (24.7)	0.005
MRI findings			
Optic glioma	0/14 (0)	5/89 (5.6)	1.000
Other brain tumors	0/14 (0)	4/89 (4.5)	1.000
Vascular abnormalities	1/14 (7.1)	4/89 (4.5)	0.526
UBO	7/14 (50)	53/89 (59.6)	0.567
Other abnormalities <sup>a</sup>	2/14 (14.3)	3/89 (3.4)	0.135
Abnormalities except UBO	3/14 (21.4)	15/89 (16.9)	0.698
Abnormalities including UBO	8/14 (57.1)	56/89 (62.9)	0.779

Values are presented as number (%) or median (range).

NF1, neurofibromatosis type 1; MRI, magnetic resonance imaging; UBO, unidentified bright object.

<sup>a</sup>Subdural hemorrhage and Chiari malformation type 1 were observed in the epileptic group and cerebral atrophy, chronic infarction, and increased volume of both hippocampi were observed in the non-epileptic group.

**Table 2.** Epilepsy characteristics in patients with neurofibromatosis type 1

Pt no.	Sex	Family history of seizure	Age at seizure onset (yr)	Seizure characteristic				MRI at seizure onset		EEG at seizure onset	No. of AED	DRE	LD
				Type	Frequency	SE	ES	UBO	Others				
1	F	+	2	Focal	0–1/year	+	-	+	Moyamoya syndrome	Normal	2	-	+
2	M	-	4.4	Focal	1/year	+	-	+		Diffuse slowing	1	-	+
3	M	-	5.8	Focal	2/week	-	-	+		Focal	4	-	+
4	M	+	5	Focal	1/year	-	SECTS	-		Focal	0	-	-
5	M	-	3.8	Focal	1/month	-	-	-		Normal	3	-	+
6	F	-	10.9	Focal	3/month	+	-	+		Focal	4	+	+
7	F	-	5.8	Focal	3/month	-	SECTS	+	Type 1 CM	Focal	1	-	-
8	M	-	18.9	Generalized	3/month	-	-	-		Normal	1	-	+
9	M	-	6.4	Generalized	10–20/day	-	CAE	-		3 Hz spike and wave	2	-	-
10	M	-	1.3	Generalized	3/day	-	-	-		Normal	0	-	-
11	M	+	5.9	Generalized	1/year	+	-	-	Subdural hemorrhage	Normal	0	-	+
12	M	-	11.1	Focal/generalized	1/year	-	-	+		Normal	0	-	-
13	M	+	7.3	Focal/generalized	2–4/day	+	LGS	+		Focal/generalized	5	+	+
14	M	+	1.1	Unknown	2–4/day	-	IS→LGS	-		Focal/generalized	3	-	+

MRI, magnetic resonance imaging; EEG, electroencephalography; AED, anti-epileptic drug; DRE, drug-refractory epilepsy; LD, learning disability; SE, status epilepticus; ES, epilepsy syndrome; UBO, unidentified bright object; SECTS, self-limited epilepsy with centrotemporal spike; CM, Chiari malformation; CAE, childhood absence epilepsy; LGS, Lennox-Gastaut syndrome; IS, infantile spasm.

epilepsy syndrome was present in five patients: Lennox-Gastaut syndrome (n = 2), self-limited epilepsy with centrotemporal spikes (n = 2), and childhood absence epilepsy (n = 1).

EEG findings at the time of seizure onset were normal in six patients (42.9%), while four (28.6%) had focal epileptiform dis-

charges, two (14.3%) had generalized, and two (14.3%) had generalized and focal. Epileptogenic zones presumed from seizure semiology and interictal EEG findings were not concordant with the location of structural abnormalities or UBOS in brain MRI of all nine patients with focal seizures (Supplementary Table 1). Among

the six patients who had follow-up MRI, findings remained normal in three patients with UBOs and one with normal findings at the time of seizure onset, although two of them still had seizures.

One patient was lost to follow-up. Among the 13 patients with follow-up data, nine (69.2%) were seizure-free for at least the last 12 months. Ten patients (71.4%) received treatment with an average of 1.9 AEDs. DRE was observed in two patients (14%): one had focal impaired awareness motor seizure or focal to bilateral seizures with seizure frequency of 1 to 3 per month and the other had Lennox-Gastaut syndrome with atypical absence, atonic, and focal to bilateral seizures despite treatment with five AEDs. Both had intellectual disability and UBOs in MRI. The UBO locations were not concordant with the location of epileptiform discharges in EEG. Five patients (35.7%) had status epilepticus and one of them died due to it.

### 3. Epilepsy risk factors in NF1

Epilepsy risk factors in NF1 were analyzed (Table 3). Age at diagnosis, sex, family history of NF1, family history of epilepsy, learning disability, and brain MRI findings including UBO and other structural abnormalities were included as variables in the multiple logistic regression analysis. The ORs of learning disability (OR, 4.54; 95% CI, 1.17 to 17.54;  $P=0.028$ ) and family history of epilepsy (OR, 39.65; 95% CI, 3.78 to 416.53;  $P=0.002$ ) were significantly higher in patients with epilepsy. Structural brain abnormalities were not found to be significant risk factors.

## Discussion

In this study, we analyzed clinical characteristics and epilepsy risk factors in patients with NF1 at a single tertiary center. The prevalence of epilepsy in NF1 patients was 13.6%, higher than the general population (0.45% to 1%) [18,19]. Our findings are consistent with previous reports regarding prevalence rates ranging between 4.1% and 14.1% [6-8,10,20,21]. Serdaroglu et al. [10] reported the prevalence of epilepsy as 4.1% among pediatric patients with NF1

from a single center in Turkey, whereas a nationwide survey in Japanese NF1 children reported 13.8% [21]. The incidence of epilepsy varied due to different cohorts and inclusion criteria used. In this study, we used data from a single tertiary care center with a rare disease and pediatric epilepsy clinics, which might have resulted in our relatively higher prevalence of epilepsy. To minimize selection bias, nationwide data under a universal criterion for the epilepsy group is needed.

Although the mechanism of seizures in NF1 has not been clarified, NF1-related intracranial pathology such as brain tumors, moyamoya syndrome, and hydrocephalus may partially explain the higher prevalence of seizures in patients with NF1 [5-7]. In addition, temporal lobe epilepsy, often associated with focal cortical dysplasia, hippocampal sclerosis, and dysembryoplastic neuroepithelial tumor, has been reported in some patients with NF1 and most have shown considerable improvement or seizure freedom after surgical resection of the epileptogenic lesion [8,22,23].

However, in this study, the proportion of structural abnormalities did not differ between the patients with and without epilepsy. Among the 14 patients with epilepsy, only three had structural abnormalities other than UBOs and their localization was not concordant with epileptogenic foci. Nine patients with focal seizures showed discordance between the location of the presumed epileptogenic zone according to seizure semiology and interictal EEG and MRI findings (Supplementary Table 1). The incidence of UBOs was not significantly different with patients with and without epilepsy (50% vs. 59.6%). Moreover, we found no relation between the localization of UBOs and epileptiform discharges on EEG in seven patients with UBOs. Furthermore, in some patients, epilepsy type ( $n=6$ , 42.9%) and EEG findings ( $n=8$ , 57.1%) were generalized. Our results are consistent with a recent study that found that the most common MRI findings in NF1 epilepsy patients are UBOs (80%), followed by normal (20%), and that the localization of UBOs and EEG abnormalities was discordant [10]. Likewise, Santoro et al. [6] reported the presence and location of UBOs were not related to seizures among the 17 patients with epi-

**Table 3.** Epilepsy risk factors in neurofibromatosis type 1

Variable	Odds ratio	95% CI	P value
Age at diagnosis	1.05	0.87–1.26	0.643
Male sex	0.26	0.04–1.58	0.144
Family history of NF1	1.13	0.23–5.62	0.884
Family history of epilepsy	39.65	3.78–416.53	0.002
Learning disability	4.54	1.17–17.54	0.028
UBOs	3.18	0.65–15.50	0.152
Other MRI findings except UBOs	0.74	0.09–5.95	0.777

CI, confidence interval; NF1, neurofibromatosis type 1; UBO, unidentified bright object; MRI, magnetic resonance imaging.

lepsy and NF1, suggesting that UBOs do not play any role in seizure pathogenesis. In a recent animal study of seizure susceptibility in NF1, a higher proportion of *Nf1*<sup>+/-</sup> mice had behavioral seizures after kainic acid or pilocarpine challenge, with shorter seizure latency and longer seizure duration, even though hippocampal damage was similar in both *Nf1*<sup>+/-</sup> and wild type controls [11]. These results suggest that in addition to structural changes, other mechanisms, such as genetic mutation, may also contribute to epileptogenesis in patients with NF1.

Several hypotheses support genetic susceptibility as a contributing seizure mechanism in NF1. Neurofibromin deficiency leads to increased Ras activity, the mechanistic target of rapamycin activation, and GABA-ergic signaling in the inhibitory circuit, which might contribute to neuronal hyperexcitability [10,24]. Neurofibromin also plays a role in cortical development, including synaptogenesis and synaptic plasticity; therefore, the lack of it may be related to abnormal cortical development and seizure development [3,25]. NF1 knockout models demonstrate abnormal cortical lamination, increased neuronal heterotopia, and microdysgenesis of the hippocampus [25], which could explain the increased occurrence of structural abnormalities such as dysembryoplastic neuroepithelial tumors and cortical malformation in some NF1 patients with epilepsy. Furthermore, the role of ion channel dysfunction leading to hyperexcitability has been suggested in NF1 mouse model [26,27]. Further study using the *Nf1*<sup>+/-</sup> mouse model will assist in determining epileptogenicity in NF1 [28].

Although the patients in our study showed heterogeneous seizure characteristics, they tended to have focal seizures (n = 9, 64.3%) and relatively good outcomes. Nine (64.3%) patients remained seizure-free for > 1 year. These findings are similar to previous studies that reported good seizure control with just one AED or without AED therapy in 60% of patients with NF1 [20,21]. Likewise, Santoro et al. [6] reported that eight of 16 patients receiving AED therapy were seizure-free for > 1 year and none had DRE. In contrast, Ostendorf et al. [7] reported that patients with epilepsy required an average of 2.4 and 3.4 medications to manage their generalized and focal seizures, respectively, and only 34% of patients were well-controlled with one or no AEDs. In our study, DRE was observed in two patients (14.3%) and both had intellectual disability and UBOs on MRI. In a study by Vivarelli et al. [29], four of 14 (29%) patients with epilepsy presented with DRE, and all four patients had severe mental retardation and three of these had malformations of cortical development. Another study including 14 patients with NF1 and DRE showed MRI abnormalities in all patients but one [30]. These heterogeneous results may be attributed to different patient characteristics including the presence of intellectual disability and structural brain abnormalities such as

cortical dysplasia and NF1-related brain tumors among the study groups, as these abnormalities can cause medically refractory seizures.

In our study, epilepsy syndrome was present in five patients: self-limited epilepsy with centrotemporal spikes, childhood absence epilepsy, infantile spasm, and Lennox-Gastaut syndrome. In addition to these, juvenile myoclonic epilepsy and Doose syndrome have been reported from the NF1 patients in previous reports [6-8]. However, no correlation between NF1 and epilepsy syndrome was found.

To determine more specific evidence of epileptogenesis in NF1, we analyzed the epilepsy risk factors and found a strong association of both learning disability and family history of seizures with epilepsy in NF1 patients. This supports a previous study that reported an increased risk of learning disability in children with NF1 and seizures [6,10]. A higher frequency of learning difficulty in the seizure group, regardless of epilepsy severity, suggests that learning disability in NF1 might co-occur with epilepsy as a genetic predisposition rather than as a causal relationship [10]. Cognitive deficits appear to be related to synaptic dysfunction because of signaling dysfunction of Ras—the extracellular signal-regulated kinase (ERK), cyclic adenosine monophosphate, and dopamine homeostasis rather than a macroscopic structural lesion [3,26]. Increased GABA-ergic signaling caused by dysfunction of Ras–ERK signaling accounts for learning deficits in an NF1 mouse model [12]. Furthermore, increased GABA-ergic signaling in local inhibitory circuits could cause seizure development by altering inhibitory/excitatory balance [26]. A higher frequency of epilepsy in family history of patients with epilepsy also supports the role of genetic susceptibility in epileptogenesis. However, only two patients in our study had a family member diagnosed with NF1 and epilepsy; therefore, other genetic predispositions to epilepsy may be related to seizure threshold in addition to the effect of the *NF1* gene. As *NF1* genetic testing in all study patients could not be performed, the association between the type and location of *NF1* variants and seizures could not be analyzed. Further studies to compare genotypes between NF1 patients with and without epilepsy may clarify the genotype-phenotype correlation.

In conclusion, epilepsy is more common in patients with NF1 compared to the general population. Although the clinical characteristics of epilepsy in NF1 are heterogeneous, most patients had focal seizures and good seizure outcome. No significant difference in structural brain abnormalities between patients with and without epilepsy was found. In addition, epilepsy in NF1 is associated with a family history of epilepsy and learning disability, which contribute to a genetic mechanism that might be associated with cellular or synaptic changes in the brain and epileptogenesis in NF1 pa-

tients. Further studies are needed to clarify the intrinsic role of *NF1* in epileptogenesis in *NF1* patients.

## Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.26815/acn.2020.00283>.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization: AS and YJL. Data curation: JCB. Formal analysis: AS. Funding acquisition: YJL. Methodology: SKH. Project administration: AS. Visualization: YJL. Writing-original draft: AS. Writing-review & editing: JCB, SKH, SK, and YJL.

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