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Epilepsy in neurofibromatosis type 1: Diffuse cerebral dysfunction?

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ABSTRACT

Introduction: Neurofibromatosis type 1 (NF1) is accompanied by epileptic seizures in 4–7% of patients. We examined clinical, electrophysiological, and radiological features associated with epilepsy in our NF1 series in order to identify risk factors.
Methods: We reviewed data of 641 pediatric patients with NF1 diagnosis according to National Institutes of Health (NIH) criteria in Hacettepe University records from January 2008–August 2018. Demographic features, NF1-related clinical and imaging characteristics, age at onset of epilepsy, seizure semiology, and frequency, electroencephalogram (EEG) findings, and response to treatment were noted.
Results: Twenty-six patients with NF1, 15 male, 11 female, had epilepsy. Age at seizure onset was 6 months to 13 years. Seizure semiology was focal with impaired awareness (n = 9, 34%), focal aware motor (n = 2, 8%), focal to bilateral tonic–clonic (n = 3, 12%), generalized tonic–clonic (n = 7, 28%), absence (n = 3, 12%), infantile spasms (n = 1), and unclassified type (n = 1). None had a history of status epilepticus. The EEG findings were normal for age in ten patients (38%). Others had focal (n = 8, 30%), generalized (n = 7, 27%), or multifocal (n = 1, 4%) discharges. On brain magnetic resonance imaging (MRI) signal intensity changes typical for NF1 (neurofibromatosis bright objects, NBOs) were the most common finding (80%), followed by normal MRI (20%). There was no relation between the localization of NBOs and discharges on EEG. Seventeen patients (65%) were seizure-free at the time of the study; 11 of them still under medication including four on multiple antiepileptic drugs. The rate of learning problems and NBO were significantly higher in patients with NF1 with epilepsy compared to those without.
Discussion: Epilepsy in NF1 is associated with relatively infrequent seizures and good response to treatment. Learning disorders are markedly frequent in this group, irrespective of the severity of epilepsy. The absence of correlation between the localizations of epileptiform discharges and lesions on MRI support the role of cellular or synaptic mechanisms rather than structural causes in the pathogenesis of epilepsy.

1. Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant single gene disorder with a prevalence of 1/3000. The *NF1* gene encodes neurofibromin, a tumor suppressor protein that regulates the RAS pathway. Other functions of neurofibromin related to phenotypic findings of NF1 involving the brain, blood vessels, or bone are not well-defined [1]. Diagnostic criteria of NF1 according to the National Institutes of Health (NIH) include cutaneous/subcutaneous or plexiform neurofibromas, café au lait macules, axillary or inguinal freckling, Lisch nodules, optic glioma, skeletal dysplasias, and a first degree relative with NF1. Cranial magnetic resonance imaging (MRI) may show focal areas of high T2-weighted signals known as neurofibromatosis bright objects (NBOs). Other findings that may accompany NF1 include vasculopathy, short stature, tendency for malignancy, macrocephaly, learning disabilities, and epilepsy. The prevalence of epilepsy in NF1 is generally reported as 4–7%, 4–5 times the prevalence described in the general population [2,3]. Its mechanisms are unclear and features are variable. We aimed to analyze the nature of epilepsy in children with NF1 admitted to our multidepartment NF1 clinic.

2. Material and methods

We retrospectively analyzed clinical notes of children diagnosed with NF1 referred to Hacettepe University from January 2000–August 2018. All patients fulfilled consensus criteria for NF1 diagnosis [4]. Epilepsy was diagnosed according to 2017 International League Against

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Epilepsy (ILAE) definition [5]. Patients with febrile seizures were excluded. Records of patients with NF1 without epilepsy were reviewed for comparison.

We retrieved age at diagnosis, family history, features of NF1 including associated clinical findings such as hypertension, macrocephaly, scoliosis, or intellectual disability from patient files and reports. Seizure semiology, frequency, and medications were noted from records and through parental interview. Seizures were classified according to ILAE recommendations. Cranial MRI findings were classified as normal, or having neurofibromatosis bright objects (NBOs), optic glioma, tumor, developmental malformation, vascular abnormality (occlusion or aneurysm), and other abnormalities. This study was approved by the ethics committee of Hacettepe University.

3. Results

3.1. Clinical characteristics

We reviewed our data of 641 patients with NF1 diagnosed before 18 years of age and found epilepsy in 26 patients, 15 boys and 11 girls (Table 1). The current age was median 12 years (5–21 years) in this group. Neurofibromatosis type 1 was present in a family member of 10 children (38%). Nine patients (34.6%) had optic glioma (bilateral n = 7, unilateral = 2). Learning difficulty was frequent (16/26, 61%). Neurofibromas (n = 10 patients, 38%), scoliosis (n = 6), macrocephaly (n = 6), hypertension (n = 2), and sphenoid dysplasia (n = 2) constituted other clinical findings.

Brain MRI was normal in 5 patients, the remaining having NBOs (80%). A cortical malformation was detected in two patients, and Moyamoya syndrome, in another two. Observed tumors were astrocytoma (n = 2), gliosarcoma (n = 1), and spinal intravascular hemangioendothelioma (n = 1).

3.2. Characteristics of patients with epilepsy

Electrographic and imaging features of 26 patients are shown in Table 2. Age at seizure onset was median 6 years (6 months–13 years).

Seventeen patients (65%) had been seizure-free for median 2 years (1–18 years). Those with ongoing seizures had a median seizure frequency of 4/month, ranging from daily to 6 monthly seizures. None had a history of status epilepticus. Eleven of seizure-free patients still received medication, including four (4/26, 15%) under multiple antiepileptic drugs. Valproate (n = 8), levetiracetam (n = 8), and lamotrigine (n = 5) were the most frequent drugs.

Seizure semiology was as follows: focal motor seizures with impaired awareness in eight (31%), focal nonmotor seizures with impaired awareness in one (4%), focal aware motor seizures in two (8%), focal to bilateral tonic–clonic seizures in three (12%), generalized tonic–clonic seizures in seven (28%), absence in three (12%), and infantile spasms and unclassified seizures, one patient each.

Electroencephalogram (EEG) findings were normal for age in ten patients (38%). Eight had focal (30%), one had multifocal (3.8%), and seven had generalized (26%, including two with 3-Hz spike-and-wave discharges) epileptic discharges.

Seizure semiology (focal/generalized) and localization of discharges on EEG were not concordant with NBOs but corresponded to the localization of brain tumors in three patients (astrocytoma and gliosarcoma).

3.3. Characteristics of patients with NF1 without epilepsy

We reviewed our database to compare clinical and imaging characteristics of patients with and without epilepsy; NF1 was familial in 271 of 481 patients (56.3%). Learning difficulty was observed in 45 of 549 (8.2%) and macrocephaly in 29 of 188 patients (15.4%).

Cranial MRI reports were obtained for 156 patients. Age at first cranial imaging was median 5 years (average 5.6 ± 3.2 years). Neurofibromatosis bright objects were observed in 77 children (49%) while 37 patients (23.8%) had a normal MRI; 24 patients (15.5%) had optic glioma. Other findings were vascular abnormality (n = 6), pilocytic astrocytoma (n = 2), and arachnoid cyst (n = 2).

Patients with epilepsy were more likely to have a learning disorder and optic gliomas. On MRI, the presence of NBO was markedly different between patients with NF1 with epilepsy and patients with NF1 without epilepsy (Table 3).

Table 1
Characteristics of our patients.

Patient	Sex	Cafe au lait spots	Axillary and inguinal freckling	Neurofibroma	Lisch nodules	Hypertension	Scoliosis	Macrocephaly	Neurocognitive profile	Family history of NF1
1*	f	No	no	No	no	no	no	no	learning difficulty	yes- cousin
2	m	Yes	yes	plexiform	yes	no	no	yes	learning difficulty	no
3	m	Yes	yes	yes	no	no	yes	no	normal	no
4	m	Yes	yes	plexiform	yes	no	no	yes	learning difficulty	yes- brother
5	m	Yes	yes	no	no	yes	no	no	learning difficulty	yes- father
6	m	Yes	yes	plexiform	yes	no	no	no	normal	yes- uncle
7	f	Yes	yes	no	no	no	yes	no	normal	no
d8	f	Yes	yes	no	no	no	no	no	normal	no
9	m	Yes	yes	no	no	yes	yes	yes	learning difficulty	no
10	f	Yes	yes	no	yes	no	no	no	learning difficulty	no
11	f	Yes	yes	plexiform	no	no	no	yes	normal	no
12	f	Yes	yes	yes	no	no	no	yes	learning difficulty	yes- uncle
13	m	Yes	yes	no	yes	no	no	no	normal	no
14	f	Yes	yes	no	no	no	no	no	learning difficulty	yes- aunt, cousin
15	m	Yes	no	no	no	no	no	no	normal	no
16	f	Yes	yes	yes	no	no	no	no	normal	no
17	m	Yes	yes	yes	no	no	no	no	learning difficulty	no
18	m	Yes	yes	no	no	no	no	yes	learning difficulty	yes- mother, brother
19	f	Yes	yes	yes	no	no	yes	no	learning difficulty	yes - brother
20	f	Yes	yes	no	no	no	no	no	learning difficulty	yes- mother, sister
21	m	Yes	yes	no	yes	no	yes	no	learning difficulty	no
22	m	Yes	yes	no	no	no	no	no	learning difficulty	yes- brother
23	f	Yes	yes	no	no	no	no	no	learning difficulty	no
24	m	Yes	yes	no	no	no	no	no	normal	no
25	m	Yes	yes	plexiform	no	no	yes	no	learning difficulty	no
26	m	Yes	no	no	no	no	no	no	Learning and behavioral	no

Table 2
Characteristics of epilepsy, EEG, and MRI features of patients with epilepsy.

Patient	Current age (years)	Age at onset of seizures (years)	Seizure frequency	Seizure-free for (years)	Seizure type	EEG	Treatment	MRI	
								NBO	Other
1	18	0.5	30/month		focal motor seizures with impaired awareness	focal	ltg, lev	+	astrocytoma, bilateral OG
2	11	8	4/month		focal motor seizures with impaired awareness	normal	lev	+	right OG
3	15	8	8/month		focal motor seizures with impaired awareness	multifocal	cbz	−	
4	14	13	1/month		generalized motor tonic–clonic seizures	normal	lev	+	nasopharyngeal mass
5	10	4	6/year		focal motor seizures with impaired awareness	normal	lev	+	bilateral OG
6	13	3	0/year	1	generalized motor tonic–clonic seizures	normal	vpa	+	
7	12	10	0/year	1	absence seizures	normal	ltg	+	
8	16	6	0/year	1	focal to bilateral tonic–clonic seizures	focal	cln, vpa	+	
9	15	7	0/year	1	generalized motor tonic–clonic	normal	ltg, pht	+	moyamoya
10	20	12	0/year	2	absence seizures	3 Hz	vpa	+	
11	9	5	0/year	2	focal motor seizures with impaired awareness	focal	ltg	+	bilateral OG L ≫ R
12	15	12	0/year	2	generalized motor tonic–clonic	normal	0	−	
13	11	2.5	0/year	3	focal to bilateral tonic–clonic seizures	focal	vpa	+	
14	12	6	0/year	4	focal nonmotor seizures with impaired awareness	focal	vpa	+	
15	5	4	0/year	1	focal motor seizures with impaired awareness	focal	lev	+	bilateral OG R ≫ L, astrocytoma
16	8	7	0/year	1	generalized motor tonic–clonic	normal	0	−	
17	9	6	0/year	3	focal to bilateral tonic–clonic seizures	focal	vpa	+	
18	13	8	0/year	5	generalized motor tonic–clonic	generalized	0	+	bilateral OG
19	20	0.3	4/month		infantile spasms	generalized	oxc	+	left MCA infarct zone, left dysplastic hemisphere, left sphenoidal bone dysplasia
20	21	1	0/year	18	unclassified seizures	generalized	0	−	bilateral OG, moyamoya, left MCA infarct zone, bone dysplasia
21	5	2.1	0/year	2	generalized motor tonic–clonic	generalized	vpa, ltg, clb	+	
22	11	10	6/year		focal aware motor seizures	focal	lev	−	left hemispheral tumor resection (gliosarcoma)
23	11	3	0/year	1	absence seizures	3 Hz	vpa	+	
24	7	6	0/year	1	focal aware motor seizures	normal	cbz	+	right OG
25	21	2.5	0/year	13	focal motor seizures with impaired awareness	normal	pb, cbz, gbp	+	chiasmatic OG, spinal neurofibroma
26	4	3	1/year	−	focal motor seizures with impaired awareness	generalized	lev	+	

cbz: carbamazepine; clb: clobazam; gbp: gabapentine; hem: hemisphere; L: left; lev: levetiracetam; ltg: lamotrigine; NBO: neurofibromatosis bright objects; MCA: middle cerebral artery; OG: optic glioma; oxc: oxcarbazepine; pb: phenobarbital; pht: phenytoin; R: right; vpa: valproate.

4. Discussion

At least one unprovoked seizure is reported in 9.5% of patients with NF1 and epilepsy, in 4–7% [2,6–10]. The prevalence may vary according to the method of data collection: a nationwide survey in 3- to 15-year-old Japanese children with NF1 reported epilepsy in 13.8% [11]. Our study, despite being from a clinical center, found a rate of 26/641 (4%) consistent with the lower end of the reported range, but still much higher than general population of Turkish children (0.8%) [12].

Table 3
Comparison of NF1 cases with epilepsy and without epilepsy.

	Epilepsy n = 26	Patients without epilepsy	P value
Family history	10	271/481	0.074
Macrocephaly	6	29/188	0.342
Learning disability	16	45/590	**≪0.001**
MRI findings			
NBO	21	76/155	**0.002**
Optic glioma	9	24/155	**0.029**
Brain tumor	4	7/155	0.055 (Fisher's exact)
Vascular abnormality	3	5/155	0.09

The exact mechanism of epilepsy in NF1 is not clear [13]. Identification of features associated with epilepsy might give clues on its pathogenesis. Our study provided the opportunity to compare children with NF1 with epilepsy and children with NF1 without epilepsy from the same center.

Neurofibromin is involved in cortical development, synapse formation, and synaptic activity, all of them important for epileptogenesis. Stafstrom et al. proposed altered excitation/inhibition balance and dysfunction of ion channels as possible mechanisms of epilepsy in NF1 [14]. Other pathways such as gamma-aminobutyric acid (GABA)-ergic signaling or mammalian/mechanistic target of rapamycin (mTOR) are also affected by an overactivated, unregulated Ras pathway. An increase in GABA is expected to reduce excitability and therefore seizures, but impair learning. The high rate of learning difficulty in the epileptic group (with epilepsy vs without epilepsy; 64% vs 8.2%) without any negative factors such as refractory epilepsy, multiple medications, or epileptic encephalopathy suggests that learning problems are not likely to result from but cooccur with epilepsy, arguing against a GABA-mediated pathogenesis [14,15].

The site of mutation within the *NF1* locus can also be related to epilepsy: duplication of the *NF1* locus has been shown to cause intellectual disability and epilepsy without any physical stigma of NF1 [16,17]. The site of duplication, also the site of microdeletion in some cases of NF1, includes many genes that, when deleted or mutated, may cause epilepsy and explain the reason why only a small percentage of patients with NF1 have seizures. Comparison of genotypes between patients with NF1 with and without epilepsy may clarify this possibility.

Other mechanisms of epilepsy in NF1 may be epigenetic, that is, microRNAs or DNA methylation silencing the gene, or alternative splicing resulting in isoforms of neurofibromin.

Neurofibromin type I, one of the major isoforms, is mostly expressed in the central nervous system and is a potent Ras regulator. Neurofibromin type II is involved in learning and memory in mouse models [18]. This issue can be explored through transcriptomic studies.

Central nervous system tumors are frequently suspected in NF1 associated with epilepsy [3]. In our group, 5 patients had intracranial tumors or cortical malformations colocalizing with discharges on EEG, supporting the role of structural lesions in a subgroup of patients with NF1 while many others had generalized or normal EEG findings, suggesting diffuse hyperexcitability.

The MRI findings predominantly consisted of NBOs, T2-hyperintensities due to vacuolar changes in myelin sheaths, which tend to resolve with age. Their focal and age-related appearance had raised suspicions for epileptogenesis, but studies found no association [7,10,19]. In our group with epilepsy, eight patients had focal epileptiform changes (32%), but focal discharges on EEG and the site of NBOs did not coincide, as reported in the literature [6]. We found similar percentages of normal MRI in patients with epilepsy and patients without epilepsy (20% and 23.8%). Neurofibromatosis bright objects are probably not directly related to epileptogenesis, but their higher rate might point at abnormalities at tissue level.

The relatively mild character of epilepsy in NF1 has also been reported by Kulkantrakorn and Geller whose series of 21 patients included many under remission [8] and by Vivarelli et al. who observed drug resistance in only 4 of 14 (29%), three of which had cortical malformations [10]. The absence of status epilepticus and the percentage of seizure-free patients support the general experience that NF1 results in a milder epilepsy than other neurogenetic epilepsies [1,2,6].

4.1. Conclusions

Patients with NF1 have an increased risk for epilepsy but a high chance of achieving remission under treatment. On the other hand, they very frequently have learning difficulties and NBOs, suggesting disturbances at synaptic or molecular level resulting in epilepsy. Further studies may clarify the epileptogenesis process in NF1.

Conflict of interest

There is no conflict of interest.

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