FULL-LENGTH ORIGINAL RESEARCH

Epilepsy in individuals with neurofibromatosis type 1

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Summary

Purpose: To describe the clinical characteristics and outcomes of individuals with neurofibromatosis type 1 (NF1) and seizures in the largest cohort reported to date.

Methods: A retrospective cross-sectional review of 536 individuals with NF1 was performed, and clinical data from 51 individuals with a history of at least one seizure were analyzed.

Key Findings: In individuals with NF1, 9.5% had a history of at least one unprovoked seizure, and 6.5% had documented epilepsy. Individuals with seizures were more likely to have inherited NF1 from their mother ($p = 0.001$). Focal seizures were the most common type, occurring in 57% of individuals, although generalized seizures, specific electroclinical syndromes, and the presence of multiple seizure types were also noted. Moreover, in 21% of individuals with a previously unremarkable magnetic resonance imaging (MRI) study, neuroimaging at seizure onset revealed a new structural abnormality. In this population, 77% of individuals required multiple antiepileptic drugs (AEDs), and some required epilepsy surgery, with the best results following temporal lobe glioma resection.

Significance: Compared to the general population, seizures are more common in individuals with NF1, where they are often focal and related to an intracranial neoplasm. These observations suggest that all individuals with NF1 and a new seizure should undergo MRI despite previous normal neuroimaging. Individuals with seizures and NF1 typically require more aggressive therapy than those without NF1 and should be considered for epilepsy surgery when appropriate.

KEY WORDS: Seizures, Brain tumor, Astrocytoma, Phakomatosis, Neurocutaneous syndrome.

The common autosomal dominant disorder, neurofibromatosis type 1 (NF1), affecting 1 in 2,500–3,000 individuals worldwide, is caused by a mutation in the *NF1* tumor suppressor gene (Friedman et al., 1999). Individuals with NF1 typically harbor multiple café-au-lait macules, Lisch nodules, axillary or inguinal freckling, neurofibromas, distinctive bony abnormalities, and optic pathway gliomas (OPGs; Riccardi, 1981; National Institutes of Health Consensus Development Conference, 1988; Friedman & Birch, 1997; Friedman et al., 1999). In addition, other neurologic problems, including malignant brain tumors, cognitive and attention deficits, headaches, and seizures are commonly encountered (Crowe et al., 1956; Huson et al., 1988, 1989; Friedman & Birch, 1997; Friedman et al., 1999; Szudek et al., 2002).

Previous reports have estimated that seizures occur in approximately 4–7% of individuals with NF1 (Riccardi, 1981; Huson et al., 1988; Korf et al., 1993; Friedman & Birch, 1997; Kulkantrakorn & Geller, 1998; Hsieh et al., 2011). This is considerably higher than the 1–2% value reported for the general population, or the 4% of children who have experienced a seizure (Hauser, 1995; Berg et al., 2010). The characteristics of seizures in individuals with NF1 have been described in smaller studies (Korf et al., 1993; Kulkantrakorn & Geller, 1998; Vivarelli et al., 2003; Hsieh et al., 2011), where an increased incidence of complex partial seizures was observed. In these studies, the authors concluded that seizures in individuals with NF1 are relatively easy to treat with antiepileptic drugs (AEDs). The purpose of this retrospective analysis was to more fully characterize the seizure type, neuroimaging correlates, and treatment strategies in the largest cohort of individuals with NF1 and seizures reported to date.

Methods

A retrospective cross-sectional review of individuals with a diagnosis of NF1 seen for any reason at Washington University Medical Center from July 1997 to December 2012 was performed under an institutional review board (IRB)–approved human studies protocol at the Washington

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University School of Medicine. Each chart was reviewed to confirm the correct diagnosis of NF1 based on established National Institutes of Health (NIH) guidelines (National Institutes of Health Consensus Development Conference, 1988). From a total of 536 individuals with NF1, 51 individuals with a history of at least one seizure event were identified. Data were collected from all chart sources, including clinician notes, individual questionnaires, electroencephalography (EEG) reports, neuroimaging studies, and surgical pathology, when available. Individual ages were determined at the time of data collection. Relative fitness is calculated as a fraction comparing the frequency of NF1 among parents of index cases with the frequency of NF1 among offspring of index cases (Tanaka, 1974). Statistical significance was calculated using chi-square test and established at $p < 0.05$.

Table 1. Parent-of-origin distribution of the entire cohort and those individuals with seizures

	Number (%)	Expected	p-Value
Cohort (327)			
Paternal	55 (17)	50	0.122
Maternal	109 (33)	94	
Spontaneous	163 (50)	179	
Individuals with seizures (45)			
Paternal	6 (13)	7	0.001
Maternal	24 (53)	13	
Spontaneous	15 (33)	25	
Individuals with epilepsy (40)			
Paternal	6 (15)	6	0.011
Maternal	20 (50)	12	
Spontaneous	14 (35)	22	

Expected values were calculated based on previous estimations of fitness.

Results

Of a total of 536 individuals with a confirmed diagnosis of NF1, 51 had a history of at least one unprovoked seizure, resulting in a prevalence of 9.5% in the total NF1 cohort aged 0.5–86 years (mean and median ages of 23 and 17 years, respectively). The first seizure occurred during childhood or adolescence in 77% of individuals, and seizures were prevalent in 12% (34/282) of those younger than age 19. The exact age of onset was documented in 38 individuals, ranging from 0.3 to 58 years and mean and median ages of 14 and 9.5 years, respectively. One person had a first seizure after age 45 years that was preceded by a left frontal lobe infarct. More males (57%) were noted to have had a seizure ($p = 0.4$). Twenty-seven (73%) of 37 individuals with documented information regarding cognition were known to have neurocognitive deficits, ranging from requiring special education classes to severe mental retardation.

Individuals with seizures were more likely to have inherited NF1 from their mother than individuals without a history of seizure, 53% versus 37%, respectively (Table 1). The overall pattern of inheritance was 33% maternal, 17% paternal, and 50% new mutations. Thirteen (28%) of 46 individuals had a family history of seizures, and 12 of those had familial data available for both NF1 and seizures. For individuals with a family history of seizures, one individual inherited NF1 from their father, 10 individuals from their mothers, and one individual had a new mutation ($p = 0.0002$). Four individuals had a history of seizures and NF1 in the same affected parent, including three in their mothers and one from their father ($p = 0.7$).

Thirty-five individuals (6.5%) had epilepsy, defined as more than one unprovoked seizure. Focal seizures were the most common type encountered, present in 29 individuals (57%) in the total cohort and in 18 individuals (41%) younger than18 years of age (Fig. S1). Six individuals had generalized seizures, with four individuals having a well-defined electroclinical syndrome, including either juvenile myoclonic epilepsy (JME; one individual) or childhood absence epilepsy (CAE; three individuals). One individual had both JME and focal seizures. Two individuals had epileptic spasms, with one subsequently developing myoclonic seizures and the other lost to follow-up.

Thirty-five individuals had a total of 64 EEG studies available, distributed across all International League Against Epilepsy (ILAE) classifications (Table 2; Berg et al., 2010). Forty-four percent of the EEG recordings were interpreted as normal. Of those EEG studies with docu-

Table 2. EEG findings in individuals with NF1

ILAE seizure classification	ECS	Individuals with EEG (%)	EEG (%)	Norm (44%)	Slow R:L:B (27%)			Epileptiform R:L:B (28%)			Gen spike/ wave (17%)	Gen slow (14%)	MF (9%)
Focal only		22 (63)	41 (64)	17	9	5	1	7	6	4	3	9	1
Absence	CAE	3 (9)	8 (13)	2							4		3
GTC only		1 (3)	1 (2)								1		
GTC, Ab, focal	JME, focal	1 (3)	3 (5)			2			1		3		
ES, myoclonic	West	1 (3)	2 (3)										2
Unknown		7 (20)	9 (14)	9									

ECS, electroclinical syndrome; Norm, normal; R, right; L, left; B, bilateral; Gen, generalized; MF, multifocal; GTC, generalized tonic–clonic; Ab, absence; ES, epileptic spasms; CAE, childhood absence epilepsy; JME, juvenile myoclonic epilepsy.

Multiple studies had more than one finding and multiple individuals had more than one EEG study, although no more than four EEG studies per individual were analyzed for this study.

mented abnormalities, 27% were focal, 19% were generalized, 5% were multifocal, and 11% had a combination of findings. Focal findings were more commonly observed in the right hemisphere, although this did not reach statistical significance ($p = 0.10$).

Brain magnetic resonance imaging (MRI) was performed on 46 individuals. Twenty-four individuals had T2-hyperintensities located in the basal ganglia, thalamus, cerebellum, or brainstem (Table 3). Other brain regions were noted to harbor T2-hyperintensities without contrast enhancement or atrophy, including the mesial temporal lobes (three individuals), subcortical white matter (two individuals), and punctate deep white matter involvement in the setting of migraine (one individual). OPGs were present in 13 (28%) individuals, and other intracranial tumors, including DNET and low-grade gliomas, were identified in 13 (28%) of individuals. One other individual had a known history of left temporal Dysembryoplastic neuroepithelial tumor (DNET) with residual encephalomalacia on MRI. Brain tumors were slightly more common on the left (six individuals) than the right (four individuals) or bilateral (four individuals). Two individuals had developmental malformations, one bilaterally and one only on the right. Developmental malformations, optic pathway gliomas, and T2-hyperintensities associated with NF1 were more commonly found in younger individuals.

Ten individuals had brain MRI performed both prior to and following their first seizure (Table 4). Four (40%) had a new finding on MRI that potentially correlated with the development of seizures. Three were unchanged, and three showed postoperative changes after removal of a tumor or the development of a T2-hyperintensity. When MRI was obtained within 1 year of a normal EEG, it was normal in 21% of individuals (4/19). Four of these subjects (21%) had new lesions that could have been attributed to their epilepsy.

Of the 47 individuals with antiepileptic medication information available, 45 had more than one documented seizure. The numbers of AEDs used by individuals with NF1-associated seizures are summarized in Table 5. No individuals were taking more than three medications. Of individuals currently taking one AED, one individual was on the modified Atkins diet and four individuals underwent epilepsy surgery. Seventeen (77%) of 22 individuals with lifetime AED data had taken more than one AED.

Eight individuals with focal seizures underwent supratentorial tumor resection or lobectomy (Table S1). Following surgery, two individuals were Engel I, one was Engel II, and four were Engel IV (two of these individuals subsequently

Table 3. Brain MRI findings in individuals with NF1 and seizures

	No. individuals (%)	Age range (years)	Mean age	Median age
UBO	24 (52)	1.5–50	10.3	9
Optic pathway glioma	13 (28)	2–40	12.1	7
Other intracranial tumors	13 (28)	4–58	23.1	17
Developmental malformations	2 (4)	3–15	7.3	4
Other	13 (28)			
Normal only	7 (15)	0.5–49	29.1	31
Total	46	0.5–72	21.2	16

"Other" included ischemic infarcts (four individuals), acute hemorrhagic infarct (one individual), diffuse atrophy (one individual), asymmetric mesial temporal lobes (one individual), left insular thickening (one individual), and T2-hyperintensities in brain regions not typically associated with T2-hyperintensities in NF1 (five individuals).

Table 4. Brain MRI findings before and after the first seizure

	Prior to first seizure		Following first seizure	
Age at first seizure	Age at MRI	Result	Age at MRI	Result
1	0.5	Normal	1.5	T2H
4	1.5	Normal	4	L brainstem mass, T2H
9	3	T2H, OPG	13	T2H, bilateral glioma
5	4	T2H, OPG	5	T2H, OPG
7	5	T2H, OPG	6	R temporal astrocytoma
7	6	R posterior fossa glioma, T2H	7	Residual tumor, T2H
<8	2	Subcortical T2-hyperintensities of U fibers	14	T2H
12	9	T2H	13	T2H
24	21	R pontine stroke	25	L frontal meningioma
58	53	L frontal infarct	58	Chronic infarct

OPG, optic pathway glioma; T2H, T2-hyperintensity; R, right; L, left.
Age displayed in years.

Table 5. Number of individuals with NF1 taking antiepileptic drugs

Medications	0	1	2	3	4	5	6	Total
Current n (%)	9 (19)	21 (45)	13 (28)	4 (9)	0	0	0	47
Lifetime n (%)	2 (9)	3 (14)	7 (32)	4 (18)	3 (14)	1 (5)	2 (9)	22

died from complications of diffuse neoplasms; Engel et al., 1993). Two individuals had surgery shortly after their first seizure, and the remainder had frequent seizures prior to surgery. Another eight individuals underwent posterior fossa tumor resection, tumor biopsy/debulking, vagal nerve stimulator or ventriculoperitoneal shunt placement, third ventriculostomy, or encephalocele repair.

Discussion

Previous studies have highlighted the increased frequency of seizures and epilepsy in individuals affected with the NF1 tumor predisposition syndrome (Korf et al., 1993; Friedman & Birch, 1997; Kulkantrakorn & Geller, 1998; Vivarelli et al., 2003; Hsieh et al., 2011). In the current report, we assessed family history, seizure frequency, type, etiology, and treatment in the largest series of individuals with NF1 to date. Similar to prior reports, we found an increased prevalence of unprovoked seizures (9.5%), which is significantly higher than that reported for individuals in the general population (Panayiotopoulos, 2010). The higher frequency of seizures in this population establishes NF1 as a risk factor for epilepsy.

Individuals with NF1 and epilepsy were more likely to have inherited NF1 from their mothers. This finding is intriguing in light of previous studies by ourselves and others, which excluded parent of origin effects on NF1 "severity" (Riccardi & Wald, 1987), T2-hyperintensities (Suenobu et al., 2008), and brain tumors (Johnson et al., 2012). It is possible that the parent of origin effect observed in our cohort reflects reduced relative fitness of males with NF1, as suggested previously (Crowe et al., 1956; Huson et al., 1989). It is important to note that our cohort, similar to others (Miller & Hall, 1978), also demonstrated an expected pattern of inheritance, based on previous reports showing that male patients with NF1 exhibit approximately half the relative fitness as female patients (Crowe et al., 1956; Huson et al., 1988). Further studies using larger numbers of individuals will be required to firmly establish the existence of parent of origin effects.

Using the recently proposed ILAE revised terminology for the organization of seizures and epilepsies (Berg et al., 2010), we determined that the majority of classifiable seizures were focal in origin. It should be noted that, in contrast to previous studies, this classification method led to a larger proportion of individuals having an unknown seizure type (30%). In individuals younger than 18 years of age, 51% had focal seizures, and 79% of classifiable epilepsies in this cohort were classified as focal. To determine the basis of this focality in the context of NF1, we examined the available EEG and neuroimaging data.

Most abnormal EEG recordings revealed focal abnormalities. In this regard, more than half of the EEG studies were abnormal, and 75% of the studies revealed focal abnormal electrical activity. Intracranial tumors (other than OPGs) were present in 28% of individuals with NF1. In addition, 67% of individuals with NF1 had T2-hyperintensities. For our analysis, we discriminated between T2-hyperintensities in the basal ganglia, thalamus, cerebellum, and brainstem and those found in the subcortical white matter or mesial temporal lobes. These latter cerebral T2-hyperintensities may be associated with an increased risk for seizures, especially those in the mesial temporal lobes. Furthermore, temporal lobe T2-hyperintensities similar in appearance on MRI to those classified by others as "unidentified bright objects" (UBOs; Hsieh et al., 2011) have been identified histologically as DNET or gliosis in other studies (Barba et al., 2013). Conversely, these MRI abnormalities may be coincidental and unrelated to NF1 or seizures, as hippocampal T2-hyperintensities have been found in healthy individuals (Labate et al., 2010). A previous report examining the frequency of T2-hyperintensities in individuals with seizures and NF1 found no association (Hsieh et al., 2011). The etiologic relationship between T2-hyperintensities and seizures, and, in some cases, the discrimination between pathologic and pathognomonic T2-hyperintensities, is unclear and warrants further investigation.

Although 50–70% of children with epilepsy in the general population are controlled on one antiepileptic drug, individuals with NF1 and seizures in our series were generally more difficult to treat with single agent therapy. Only 16 individuals (34%) were well-controlled with one or no AED therapy, and 59% of individuals with lifetime AED data had been on three or more medications or underwent epilepsy surgery. In this regard, individuals with NF1 required an average of 2.4 and 3.4 medications to manage their generalized and focal seizures, respectively. This finding is in contrast to previous studies reporting that 60% of individuals with NF1 had good seizure control on one or no AED therapy (Korf et al., 1993; Kulkantrakorn & Geller, 1998).

Overall, these observations suggest that individuals with NF1 and seizures may be good candidates for epilepsy surgery. Further supporting our findings, in a series of 12 individuals with NF1 who were undergoing surgery for epilepsy, eight were seizure-free at 1-year follow-up, and another individual had decreased seizure burden (Barba et al., 2013). However, further study is necessary to determine the safety and efficacy of surgery as well as to

define the clinical, radiographic, and electrophysiologic characteristics of those individuals who would benefit most from surgery. Although it is possible that ascertainment bias was introduced in our series, since the majority of individuals with NF1 in our cohort were seen at a tertiary care center (similar to previous reports), it is more likely that this finding reflects the high incidence of focal abnormalities and low-grade neoplasms on MRI, an established risk factor for refractory epilepsy (Hildebrand et al., 2005; Wick et al., 2005). Furthermore, 40% of individuals with MRI both before and after their first seizure had a new significant lesion. This observation, coupled with the high frequency of intracranial neoplasms found in individuals with NF1 and seizures, should prompt clinicians to obtain neuroimaging following a first-time seizure, even if previous imaging was unremarkable.

Our study highlights the relatively high prevalence of seizures in individuals with NF1. In addition, most seizures arising in the context of NF1 are focal in origin, perhaps related to underlying structural brain lesions occurring in this brain tumor predisposition syndrome. These observations support the use of neuroimaging to exclude possible neoplastic etiologies in this at-risk population, and the need for referral to an epileptologist to ensure optimal AED or surgical control of seizures in individuals with NF1.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Seizure types in individuals with NF1.

Table S1. Characteristics of individuals with NF1 who underwent intracranial surgery or vagus nerve stimulator (VNS) placement.