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ORIGINAL PAPER

Neurofibromatosis type 1 and infantile spasms

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Abstract
Background There is no agreement on the prevalence, natural history and outcome of infantile spasms (IS) in neurofibromatosis type 1 (NF1). By contrast, its prevalence and outcome are well characterised in the setting of other neurocutaneous disorders (e.g. tuberous sclerosis).
Materials and methods The aim of the present study was to try to establish a genotype–phenotype correlation in IS in the setting of NF1. A retrospective (years 1990–2000) and prospective (years 2000–2006) study in three paediatric centres in Italy were taken as referral populations for: (1) children with NF1 and (2) neurological problems in childhood.
Results Ten NF1 patients have had IS. The calculated population-based: (1) prevalence of IS in NF1 (0.76%) was higher than the reported frequency of IS in the general population (0.02–0.05%) and (2) frequency of NF1 in the IS series in two out of three centres (0.62–0.90%) was lower than the estimated frequencies in the literature (1.5–3.0%). Patients had psychomotor delay preceding the spasms (50%), symmetrical spasms (50%), typical (80%) and modified (20%) hypsarrhythmia and foci of spikes and waves and a good response to corticosteroid treatment (50%). Outcome was good in 30%. Imaging revealed high-signal foci in atypical locations (sub-cortical and central brain regions). Deoxyribonucleic acid analysis revealed three novel NF1 gene mutations without genotype–phenotype correlation.
Conclusion Even though the combination of IS and NF1 does not seem to be coincidental, it is certainly an unusual event in NF1—rarer than in other neurocutaneous disorders. Spasms in NF1 are not associated with specific genetic defects.

Keywords Neurofibromatosis · Infantile spasms · Developmental disorders

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Introduction

Neurofibromatosis type 1 (NF1; OMIM#162200) [1] is one of the commonest autosomal dominant disorders with a prevalence of 1 in 4,000 individuals in the general population [2, 3]. It is an extremely variable condition whose morbidity and mortality is largely dictated by the occurrence of complications, which are numerous and can involve any of the body systems [2–5]. The last two decades have witnessed mapping and molecular cloning of the NF1 gene to chromosome 17q11.2 and identification of its protein product neurofibromin, a modulator of ras-mediated cell proliferation [6, 7]. Attempts to establish genotype–phenotype correlations have so far identified two specific sub-groups: (1) large NF1 gene deletions associated to more severe phenotypes including dysmorphic features, mental retardation and earlier occurrence of neurofibromas and (2) the so-called NF1 micro-deletion syndrome accompanied by increased occurrence of larger (plexiform) neurofibromas and malignant transformation of neurofibromas [1, 6, 7].

The involvement of the nervous system in NF1 mainly consists in learning disabilities, plexiform neurofibromas, megalencephaly, cerebral tumours, headache, acqueductal stenosis, cerebrovascular disease, meningoceles, neurofibromatous neuropathy and cerebral high-signal lesions on T2-weighted magnetic resonance images [2, 3, 5, 8, 9]. Some authors had unquestioningly accepted in the past that epilepsy was one of the most common neurological complication in NF1 [2, 5, 10–12]. More recent NF1 population-based studies suggested, however, that seizures may be relatively uncommon in NF1 (calculated frequency= 3.3%) and not always explained by underlying brain lesions [2–5, 13, 14].

Infantile spasms (IS) are the most frequent cause of epilepsy in infancy, with incidence rates ranging from 2 to 5 per 10,000 live births [11, 15–19]. Spasms typically are sudden, usually bilateral tonic–clonic contractions of the muscles of the neck, trunk and extremities which may be flexor, extensor or mixed and are sometimes isolated but characteristically occur in clusters. Hypsarrhythmia is the most remarkable associated electroencephalographic (EEG) pattern: The triad of IS (as a seizure type), hypsarrhythmia and mental retardation is referred to as IS syndrome (West syndrome). IS have been conventionally classified into primary or symptomatic according to lack or demonstrated etiologic cause: A third category of cryptogenic IS refers to children who have developmental delay or an abnormal neurological examination before the onset of spasms but in whom an aetiology cannot be identified with current investigations [19]. Molecular genetic studies have identified so far an underlying defect in one familial form of X-linked IS (ISSX; OMIM#308350) [1, 5, 20] by finding abnormalities in the aristaless-related homeobox gene (ARX) which maps to chromosome Xp21.3-p22.1 and causes in humans various forms of epilepsy, including IS, myoclonic seizures and peripheral dystonia as well as syndromic and non-syndromic X-linked mental retardation and lissencephaly with abnormal genitalia (OMIM#300382) [1, 5].

The prevalence and outcome of IS are well characterised in the setting of most neurocutaneous disorders (e.g. tuberous sclerosis [TS], etc.) [15–19, 21]. By contrast, still there is no agreement on the frequency and natural history of IS in NF1 [2–8, 14, 17–19]. In addition, no attempt has been made so far to try to establish genotype–phenotype correlations between these conditions [1–3, 5–7].

To better define the clinical, EEG and imaging features and outcome of IS in NF1 and to try to correlate genotype with phenotype findings, we studied the clinical, imaging and molecular data in a series of ten NF1 patients with IS followed up in three University paediatric centres in northern (Padua) and central (Rome) and southern (Catania) Italy.

Subjects and methods

The Catania and Padua neurofibromatosis (NF) clinics cater to families with all forms of NF referred for diagnosis, management advice, and genetic counselling from all the eastern Sicilian (Catania) and northern–eastern Italian (Padua) regions. The majority of patients are from the Catania and Padua provinces, respectively (approximate populations 2.9 million inhabitants each region). In both centres, NF subjects are referred from all the city hospitals, the general paediatricians and general practitioners, the regional neurofibromatoses lay group associations and the consultants in dermatology, paediatrics, neurology, genetics and neuroradiology in either towns. The hospitals, the lay groups and the practitioners and consultants are yearly contacted via letters for referrals.

From November 1990 to January 2006, 1,050 children with NF1 were independently seen and followed up in Catania (n=497; 284 boys, 213 girls; aged 9 months to 17 years) and Padua (n=553; 318 boys, 235 girls; aged 6 months to 18 years). Diagnosis of NF1 was made according to the NIH Consensus conference criteria revised by the National Neurofibromatosis Foundation consortium [22–24]. Children had a general medical review as indicated, to monitor a disease complication [23, 24]. No policy of further investigations was defined after 1995, and the further approach of patients depended on the physician's findings and on patient's acceptance according to the Italian [24] and International protocol [22, 23] of NF1. Specifically, EEG and neuroimaging investigations were performed if there was a suggestion or evidence of neurological and/or psychiatric complications.

The paediatric neurology units in Rome and Catania cater to neurologically ill children from the eastern provinces of Sicily (Catania) and Lazio (Roma; approximate populations of 2.9 and 1 million inhabitants, respectively; 2,600 to 2,700 outpatient referrals per year during period 1998–2002 for each centre). The centre in Catania is the solely referral centre for the town of Catania.

Cases were independently and prospectively followed up in Catania and Padua and retrospectively gathered from the centre in Rome. In each centre, we reviewed the files of patients referred in the period comprising between 1982 and 2002 for initial treatment of IS. Clinical notes, EEG tracings, anti-convulsant protocols and neuroimaging (computed tomography and/or magnetic resonance imaging [MRI] scans) studies were reviewed. All the patients with NF1 and IS were re-evaluated in each centre between October 2000 and July 2006 by one of us (Ruggieri). All patients had an MRI scan. All the NF1/IS patients underwent standard EEG recording at the time of diagnosis and video EEG recording during the diagnostic workup.

The age-related neuropsychological workup consisted of administration of cognitive and behavioural tests including Wechsler Intelligence Scale for Children—Revised, Wechsler Adult Intelligence Scale and Bender visuo-spatial tests [25].

For their specific setup (as explained above), Catania and Padua were taken as prevalence samples for children with NF1 and Catania and Rome as prevalence samples for neurological problems in childhood.

Cytogenetic and DNA analysis

Cytogenetic analysis was performed by means of standard karyotype study and fluorescence in situ hybridisation analysis of the NF1 gene. DNA from all the NF1 subjects with IS was extracted from peripheral blood leukocytes. Genomic DNA was isolated, from total blood samples using a standard protocol as published elsewhere [6]. For polymerase chain reaction amplification of the 60 exons of the NF1 gene, primers were used as previously described [6], and samples were analysed by means of denaturing high-performance liquid chromatography analysis and DNA sequencing as reported elsewhere [6, 26].

Results

A total of ten NF1 subjects affected with IS have been identified: Table 1 summarises their findings.

Two of these ten patients were born and lived in Catania (case 1) and Padua (case 4), respectively. The remaining eight patients were referred either to the NF centre in Catania (n=5) by consultants of the region Sicily (cases 3, 6, 7 and 10) and Calabria (case 2) or to the paediatric neurology unit in Rome (n=3) by consultants in the region Lazio (case 5) and Tuscany (cases 8 and 9).

Cognitive and behaviour regression/worsening was concomitant with the onset of spasms in seven patients: mild to moderate in four and substantial in three.

Spasms were frequent in eight patients. Early cessation of the spasms was noted in cases 2 and 5. No children had other types of seizures before spasms. EEG showed typical (n=8) and modified (n=2) hypsarrhythmia.

In case 2, spasms disappeared 3 days after treatment with adrenocorticotropic hormone (ACTH; see below). The remaining nine cases were treated with ACTH (100 mg administered at one third of the dose for 15 days tapering one third of the dose every alternative day for further 15 days) with good response in four, whatever the time lapse from onset of spasms, and then switched to other anticonvulsants (specifically, valproic acid 20 mg kg^{-1} day^{-1}, vigabatrin 40–80 mg kg^{-1} day^{-1} and lamotrigine 5 mg kg^{-1} day^{-1}).

Four patients remained seizure-free without relapses after discontinuation either of ACTH or specific anticonvulsant therapy. Seven patients had classic anticonvulsant treatment for 2 to 10 years. Lennoux–Gastaut type of seizures was observed in two patients. One child had complex partial seizures with mild to good response to treatment, and another child had intractable myoclonic seizures at her last follow-up control and two generalised tonic clonic seizures (Table 1).

Brain MRI scans showed the typical high-signal lesions of NF1in three patients (Table 1); Three patients revealed high-signal foci in the subcortical white matter associated to enlarged subarachnoid spaces and slight ventricular dilatation.

Outcome was good in three cases: All were of normal intelligence with no behavioural problems at follow-up and attended school with good profit.

The IS frequency in the NF1 population (defined as the proportion of NF1 subjects with IS resident in the areas covered by the Clinics in Catania and Padua among the total NF1 subjects resident in the same town areas) was estimated to be 0.76% (2 of 260), considering only cases 1 and 4 living in Catania and Padua (out of a total of 260 NF1 subjects resident in either areas), to avoid ascertainment bias due to higher probability to be referred to these second-level clinics of the IS cases living in other regions. Notably, no new cases of IS were recorded in the NF1 populations of these two centres in the last 4 years (out of 50–60 new diagnoses per year in each centre).

Cytogenetic and DNA results

Germ-line mutations were identified in nine of ten subjects: Three of these alterations were novel including nucleotide

Table 1 Clinical, EEG and neuroimaging features of 10 individuals with NF1 and infantile spasms

Features	1	2	3	4	5	6	7	8	9	10
Sex	M	F	M	F	M	F	M	M	F	M
Age (years)	2	5	5	12	11	12	13	21	22	26
NF1 features										
Major										
CAL spots	+	+	+	+	+	+	+	+	+	+
Freckling	–	+	+	+	+	+	+	+	+	+
Lisch nodules	–	–	–	+	+	+	+	+	+	+
Neurofibromas	–	+	+	+	+	+	+	+	+	+
Minor										
Macrocephaly	+	+	–	+	–	+	+	–	+	–
Short stature	–	–	–	+	–	+	–	–	+	–
Thoracic	+	–	–	+	–	+	–	–	+	+
Complications	–	Scoliosis	–	Scoliosis	–	–	OPG	–	Scoliosis, AS	Scoliosis
NF1 family history	+	–	–	–	+	–	–	–	+	–
Familial epilepsy	–	–	–	–	–	–	–	–	–	–
Perinatal period	N	N	N	N	N	N	A	N	A	N
Development prior to IS	N	Mild delay	Delay	N	N	Delay	N	N	Delay	–
Age at seizures (months)	6	6	7	8	8	3	4	7	9	5
Type of spasms	Asymm. Flexion arms, trunk	Symm. Head nods	Symm. Mixed f/e arms	Symm. Mixed f/e limbs, trunk	Asymm.	Symm.	Asymm. Mixed f/e	Symm. Flexion arms, trunk	Asymm. Mixed f/e	Symm. Mixed
Focal signs	+ (eye)	–	+ (mouth)	–	+ (eye)	–	+	–	+	+
Interictal EEG	Hyps.	Hyps	Hyps.	Hyps.	Hyps.	Hyps.	modified	Hyps.	Modified	Hyps
EEG (focal features)	+	–	–	–	–	+	–	–	+	–
Steroid response	Poor	Good	Good	Good	Good	Poor	Poor	Good	Poor	Poor
AED response	Poor	–	–	Mild/good	–	Poor	Poor	Good	Poor	Poor
Neuroimaging	N	UBO, BG, MES, CB	UBO	UBO	N	Sc BF, EV	Sc BF, EV	N Sc BF, EV	N	
Last seizure type	LGS	–	–	CPS	–	Myocl.	GTCS	–	LGS	GTCS
Outcome	Poor (DD)	Good	Mild MR	Mild DD good	Good	Severe MR	Mild MR	Good	Severe MR	Mod MR

A Abnormal, *M* male, *F* female, *N* normal, *Hyps* hypsarrhytmia, *UBO* high-signal lesions on T2-weighted images, *Sc BF* subcortical bright foci, *EV* enlarged ventricles, *BG* basal ganglia, *MES* mesencephalon, *CB* cerebellum, *LGS* Lennox–Gastaut syndrome, *CPS* complex partial seizures, *GTCS* generalised tonic clonic seizures, *DD* developmental delay, *MR* mental retardation, *OPG* optic pathway glioma

substitutions (L1109F; $n=1$), small deletion (1503delG; $n=1$) and small insertions (1504insA; $n=1$). None of the novel mutations was detected in 100 control chromosomes from a group of healthy individuals from the same Italian regions [26]. No large gene deletion was identified in the subjects analysed.

Discussion

This study on IS in NF1 suggests that IS occurs in NF1 with a frequency (0.76%) ten- to twenty-folds higher [27] than that reported in the general population (0.02–0.05%) [11, 17–20, 28–31]. These figures are also higher than those recorded for IS in previous population-based NF1 studies (0.2% to 0.3%) [2, 3, 5, 13, 14] but lower than figures recorded in previous hospital-based NF1 series (1%) [12, 32–37]. The calculated frequency of NF1 in the IS series in Catania and Rome was 0.62% (1 of 160) and 0.90% (1 of 110), respectively—certainly high but lower than the estimated frequency of NF1 in IS series in the literature (1.5–3.5%) [11, 17–20, 28–31]. All these prevalence figures are certainly alleviated by the overall number of NF1 subjects with IS. In addition, an ascertainment bias towards second-level referrals either for NF1 and IS could not be entirely excluded. Despite these considerations, we could conclude that IS in the setting of NF1 is an unusual event (6 cases out of 1,050 NF1 patients seen over 16 years in the NF1 centres of Catania and Padua)—certainly rarer than in other well-known neurocutaneous disorders. In addition, by literature review [9, 10, 12, 14, 21, 34, 36], we recorded scanty cases of IS in the setting of NF1.

The neuroimaging findings in these NF1 patients with IS were peculiar in that the high-signal foci seen in the brain (Table 1) were prevalently either sub-cortical or mostly located in the higher portions of the brain stem and central cerebral regions (e.g. mesencephalon; 44.4% observed in our cases vs. 10% expected in the general NF1 population) [2, 3, 5, 35, 38, 39]. We found no apparent explanation to such phenomenon. It must be noted, however, that these foci were first detected on brain MRI scans after the age of 3 years (as typically occurs in NF1) [38, 39], thus, their possible role in the pathogenesis of spasms could be marginal. The slight cerebral atrophy found in three out of these ten NF1 patients was most likely related to corticosteroid administration. This atrophy reverted to normal after withdrawal of therapy.

There was no apparent correlation between IS and severity of the NF1 phenotype: Patients with severe IS had a mild NF1 phenotype and vice versa with no significant figures in each group (Table 1). In addition, we could not record dysmorphic features or differences in onset and clinical behaviour of the typical NF1 features and disease complications in these NF1 cases with spasms [40]. No specific genotype could be correlated with the epileptic or overall phenotype in this series. This is in contrast to what has been recorded in TS where IS have been associated with a more severe neurocutaneous phenotype harbouring mutations/deletions of the TSC2 gene vs. the TSC1 gene [1, 41].

Interestingly, two of these ten patients were treated with vigabatrin as first-line therapy with poor or fair seizure control; both patients were thereafter put under treatment with corticosteroids with better seizure control.

On the basis of clinical and imaging findings, these cases of IS and more in general IS in the setting of NF1 could be classified as intermediate between cryptogenic and symptomatic IS [11, 17–19]. This is in contrast with other reports suggesting that IS in NF1 were either idiopathic [34] or symptomatic [13, 14, 21]. Our assumption is based on the lack of a responsible/defined pathologic event for IS in NF1 in the setting of a demonstrated neurological (neurogenetic) disorder (i.e. NF1). Thus, any comparison (in terms of seizure, EEG phenomena, management and outcome) with other neurocutaneous disorders with spasms (e.g. TS, Sturge–Weber syndrome, etc.) could be not entirely appropriated.

Disclosure The authors report no conflicts of interest.

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