Long-term outcomes of Functional Neurological Disorder in children

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Abbreviations

CAMHS	Children's and Adolescents' Mental Health Services
DSM	Diagnostic and Statistical Manual
FND	Functional Neurological Disorder
ICD	International Classification of Diseases
IDACI	Income Deprivation Affecting Children Index, part of IMD
IMD	Index of Multiple Deprivation (see text)
NHS	(UK) National Health Service
NTW	Northumberland Tyne & Wear NHS Foundation Trust (a provider of specialist paediatric mental health services (CAMHS: see text)
NUTH	Newcastle upon Tyne Hospitals NHS Trust (a University Hospital providing adult and paediatric medical services: see text)

What's known on this subject
Functional Neurological Disorder (FND) is a major challenge in both paediatric and adult neurological practice.
Although reported short term outcomes after paediatric FND have been encouraging, very little is known about long term outcomes

What this study adds
The incidence of paediatric FND is higher than previously reported, due to co-occurrence of FND with conventional neurological disease (especially epilepsy).
Even in a selected population of children reaching specialist paediatric neurology services a high long-term symptom remission rate is seen

Contributors' Statement Page

Dr Forsyth conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, carried out the initial analyses and reviewed and revised the manuscript.
Drs Raper and Currigan and Ms Fothergill designed data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.
Prof Stone designed the study, carried out the initial analyses and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objectives

To establish the incidence and long-term outcomes (up to 21 years) of children presenting to a University hospital paediatric neurology service with symptoms due to functional neurological disorder (FND) with particular reference to occurrence of FND or similar symptoms in adulthood

Methods

Retrospective chart review to determine characteristics of the original paediatric FND presentation plus record-linkage with providers of Child and Adolescent Mental Health Services (CAMHS). Chart review of adult medical records for documentation of functional symptoms in adulthood

Results

124 individuals (56% female) met entry criteria. The most common presentations were seizures (18%), sensory loss (18%) and motor symptoms (16%). Frequency gradually increased with age of onset with an incidence in paediatric neurological services of 6 per 100,000 children under 16. In up to 21 years' follow-up (median 8.3 years), 114/124 attained their 16th birthdays by the study census date and were thus eligible for inclusion in an analysis of symptom persistence/recurrence in adulthood. 26/114 (23%) showed evidence of FND in adulthood of sufficient significance to be recorded in medical records.

Conclusion

Paediatric FND is commoner than previous estimates. Even in this selected population of children reaching specialist paediatric neurology services a high long-term remission rate is observed.

Introduction

Functional Neurological Disorder (FND) is a diagnostic term for the various ways in which patients experience abnormalities of nervous system functioning that are internally inconsistent, or incongruous with recognised brain pathology. Past, mostly less constructive synonyms have included “hysterical”, “conversion”, “psychogenic”, “non-organic”, “medically-unexplained”, “dissociative” and “somatoform” symptoms. FND is common in adults: responsible for 7-15% and playing a role in up to a third of all new referrals to adult neurology clinics[1-3]. FND can be reliably diagnosed by the presence of positive, characteristic clinical features: it is not merely a diagnosis of exclusion, turned to as organic causes for symptoms are eliminated[4,5].

Although there has been some research into general functional symptoms in childhood there has been little specific focus on paediatric functional *neurological* symptoms. Lieb et al. found 12.5% of 14-24 year olds reporting “general somatoform symptoms”[6]. Using a surveillance approach, Ani et al[7] reported an incidence for “conversion disorder” of 1.30/100,000 children under 16 years of age. Their case definition is one that will have emphasised neurological presentations. They found an incidence of 0.26/100,000 in children under 10 and 3.04/100,000 in 10-15 year olds and a 3:1 female to male ratio in both age groups[7]. Kozlowska *et al* estimated an incidence of 2.3-4.2/100,000 of “conversion disorder” presenting to paediatricians: again neurological symptoms predominated although other presentations were seen[8].

Prognosis in adult FND is guarded, with remission rates for motor and seizure symptoms of 21% and 40% respectively[9]. Corresponding outcome data in paediatric FND is limited although short-term outcome appears reasonably favourable[7,10,11]. Reported symptom

freedom rates after non-epileptic seizures in children vary widely from 23-72%[12]. The limited longer-term outcome data however is less sanguine. Jans et al.[13] reported late outcomes in a selected cohort of children with dissociative symptoms (mean age at presentation 11.7 years) with 83% meeting criteria for various psychiatric diagnoses and 26% still suffering dissociative symptoms 12 years later. A Finnish study found strong correlation between frequent reporting of somatoform symptoms in teenagers (mean age 16.8 years) and continued reporting of those symptoms five years later[14]

Prolonged duration of symptoms and delayed recognition of their functional nature emerge as negative prognostic factors in adult studies[15]. This suggests that adults with FND symptoms that have persisted since childhood may be a particularly challenging group to help. Thus we hypothesise that an improved understanding of factors associated with persistence and/or relapse of FND after paediatric presentations may have relevance to the study of FND at all ages.

In this study we examine late outcomes (up to 21 years) after paediatric presentations of FND to a single University Hospital paediatric neurology service.

Methods

Case ascertainment

Index cases were identified from a diagnostic database maintained in Newcastle of all in- and out-patients seen by the Paediatric Neurology service at the Newcastle upon Tyne Hospitals' NHS Foundation Trust (NUTH) since 1997. Up to five diagnosis fields are available for each patient in the database and ICD-10 is used as the coding system. Coding was performed prospectively by RF throughout this period. The Service sees tertiary referrals from an area of northern England with a under 16 population in 2011 of 601,263[16]. The same hospital is the sole hospital provider of adult medical services (including neurology) to a geographically smaller area around Newcastle. To minimise the potential for bias due to more straightforward adult functional presentations elsewhere in the region being seen and managed locally and thus absent from adult NUTH records, we selected children resident at presentation in a restricted area around the hospital comprising Newcastle, Northumberland, and North Tyneside (with a combined under-16 population in 2011 of 137,553).

The primary sample therefore comprised all children in the database with one or more of their up to five ICD-10 diagnoses in the range F44.x ("Dissociative [conversion] disorders"), F45.x ("Somatoform disorders") or F48.x ("Other neurotic disorders": including "neurasthenia" and "de-personalisation-derealization syndrome"); resident in Newcastle, Northumberland, or North Tyneside; presenting between 1st February 1997 and 31st December 2017.

Baseline Data extraction

Data relating to the initial FND presentation were extracted via chart review by JR. Age at symptom onset and time from symptom onset to recognition of the FND diagnosis, gender,

details of initial presentation and presence of any co-morbidities were recorded. Where multiple symptoms were present a “dominant” symptom was identified by JR based on the primary presenting complaint and/or the symptom causing greatest limitation. Family socioeconomic status was inferred using the Income Deprivation Affecting Children Index (IDACI)[17], a locality deprivation score combining census-derived indicators of income, employment, health, and disability calculated from the family postcode at the time of presentation.

Two raters (JR and VC) independently coded “nature of explanation offered for symptoms” and “parental acceptance of proposed functional nature of symptoms” using the classification in

Table *2*. Coding discrepancies were reconciled by discussion.

Follow-up methods

The NUTH medical records for these individuals subsequent to the FND presentation were examined by a single rater (JR) for any evidence of contact with adult medical services for FND or a functional disorder affecting any another body system, prior to a census date of 31st December 2017. Such contact was defined as "relapse" and was the primary endpoint for statistical analyses.

Additionally, we undertook a record linkage study with Northumberland, Tyne & Wear NHS Foundation Trust (NTW), the provider of mental health services to the same geographic population, to allow identification of involvement with NTW Children's and Adolescents' Mental Health Services (CAMHS) and start and end dates of such involvement. Contact with CAMHS was coded as "before" (CAMHS involvement had ended prior to the diagnosis of FND), "after" (CAMHS involvement commenced subsequent to diagnosis of FND), "spanning" (began before and continued after diagnosis of FND), or as "no record of involvement".

Statistical analysis

A right-censored, left-truncated Cox proportional-hazard model was used to determine factors associated with presentation to adult medical services with FND with cases being informative once they were over 16, using a censor date of 31st December 2017. Cox proportional-hazard models are well-suited to left-truncated data, necessary here as children could only become cases capable of "relapsing" (i.e. presenting to adult services) once they were 16. All potentially relevant clinical data reliably and widely ascertainable from clinical

notes were used as independent variables in the model. Survival analysis was performed using the *survival* library[18] in R[19] and all other analysis performed in R. Standard methods were used for the calculation of inter-rater reliability[20], Kruskall-Wallis[21] and Pearson chi-squared tests[22].

Ethics

Regulatory approvals were sought for both the notes review of former patients, and the record-linkage to be completed without explicit informed consent from past patients. This was felt to be important as (i) contacting patients many years after diagnosis, who may not self-identify as having experienced FND was regarded as potentially psychologically harmful; and (ii) there was a major risk of bias if only records of individuals giving explicit consent were available. Support for this position came from a public consultation exercise conducted with the help of FND Action, a UK patient support organisation for individuals affected by FND (www.fndaction.org.uk). In an online survey (n = 42 responses) 80% strongly or somewhat agreed with the study design and its rationale. Approvals were granted by the North East Newcastle & North Tyneside 1 Research Ethics Committee (reference 16NE0401) and the national Confidentiality Advisory Group of the NHS Health Research Authority (reference 17/CAG/0047).

Results

Baseline data

124 individuals (70 female) met study criteria, an incidence of 6.0/100,000 children under 16 (see Discussion). Characteristics are shown in

Figures

Figure *1* and Table 1. FND became gradually more common with increasing age of onset such that the modal age of onset was 16 years. Non-epileptic seizures were the commonest presentation (41%) followed by sensory loss (18%), motor symptoms (predominantly limb weakness: 16%), pain (11%) and other (14%). A minority of presentations (13/124) were poly-symptomatic, the commonest combination being of pain with sensory loss (n = 6). In these cases, the dominant symptom was recorded. There was no statistically significant association between presentation symptom group and sex ($p>0.4$) (Figure 2). In 18 cases a precipitating organic "trigger" for the FND presentation could be identified (minor injury in 5, syncope in 5, migraine in 3, other in 4) however since absence of such documentation could not be assumed to be documentation of absence, this factor could not be used in subsequent analysis.

Neurological co-morbidities were common (Table 1). In those in whom other neurological diagnoses were considered (usually at other centres) before a functional diagnosis was made (n = 44), epilepsy was by far the commonest (Table 1): the “other” group here comprised often-tentative diagnoses made in other centres (usually in single cases) including neuropraxis, Alice in Wonderland syndrome, cervical rib, paroxysmal extreme pain syndrome, and optic neuritis. Chronic non-neurological medical conditions (hypermobility, asthma, diabetes, arthritis etc) were present in 16 children (data not shown).

Consensus codings for the explanation model provided and parental acceptance are shown in

Table *2*. The inter-rater kappa reliability statistics[20] for the independent ratings of these two variables were 0.81 and 0.71 respectively indicating substantial agreement. There was insufficient data available in the medical records to categorise "explanation given" for n = 9 and "parental response" for n = 58 cases. There was no statistically significant association between these two factors (i.e. no evidence that particular explanation models were associated with greater parental acceptance; $p > 0.3$ after combining the first with second and third with fourth parental response categories to address small numbers).

Time to diagnosis (the interval from symptom onset, which sometimes had to be estimated, to the point at which a functional diagnosis was made) was highly skewed and ranged from 0 – 1866 days (median 200, IQR 83-413 days) (Table 1). Although the majority of the very long diagnostic delays were situations of non-epileptic seizures developing on a background of established epilepsy, associations between symptom group and time to diagnosis did not reach statistical significance (Kruskal-Wallis rank sum; $p = 0.86$). There was however evidence of longer times to diagnosis for females (median, range and interquartile range 240, 11-1866, 96-605 days) than males (152, 0-708, 52-392 days) (Kruskal-Wallis rank sum; $p = 0.048$). Time to diagnosis was greater in the "hostile" than in other parental response groups (Kruskal-Wallis rank sum; $p = 0.028$) although the direction of causality here cannot be established: parental distress may be a *result* of delayed diagnosis.

Follow up data

Initial follow up practices within the paediatric neurology service varied widely with periods of active ongoing neurological involvement after diagnosis of FND ranging from 0-74

months (median 3.4, IQR 0-14 months). A wide variety of other services (clinical psychology, physiotherapy, pain team, other medical specialties) were typically involved during this time. The more rapid discharges typically reflected transfer back to secondary paediatric or mental health services for ongoing management after confirmation of a diagnosis of FND. Roughly a third (40/124) of cases were deemed to be in remission at the time of discharge from paediatric neurology. There was no statistically significant association between presenting symptom group and either duration of follow up with, or remission at discharge from, paediatric neurology services (data not shown). Commonest referral destinations for ongoing support were general (secondary) paediatrics (n = 24), and clinical psychology (n = 28). Decisions as to whether refer on for more substantial CAMHS support were at treating clinicians' and clinical psychologists' discretion.

We found documentation of CAMHS involvement for 64/124 patients. 6/124 had had CAMHS contact that had ended before the FND diagnosis and had not continued afterward. 25/124 had confirmed involvement only after their FND was diagnosed. 33/124 had documented involvement that had commenced before and continued after the FND diagnosis. There was no documentation of CAMHS involvement for 60/124. For patient confidentiality reasons we did not seek to access primary CAMHS medical records.

114 of 124 individuals were over 16 on 31st December 2017 and thus potentially able to present to adult medical services. Evidence of contact with adult medical services with functional symptoms was found for n = 26/114 (23%). 18/26 presented with a relapse of the same symptom(s) exhibited in childhood. 8/26 presented with a different symptom. Two with previous subjective sensory symptoms developed non-epileptic attacks or collapses. One with previous non-epileptic attacks developed functional visual loss, and another *vice versa*. Two

individuals presented with new non-neurological functional symptoms: one had been seen by orthopaedics with chronic back pain and one by nephrology with loin pain. These eight included four individuals who remained under paediatric neurology follow up for persisting functional symptoms at the time of transition to adult services. Three of these had non-epileptic seizures alongside epilepsy.

Periods of symptom freedom (from diagnosis of FND to the earlier of either first relapse after age 16 or 31st December 2017) ranged from 0 to 20.8 years (median and IQR: 8.3 (4.5 -12.4 years)). Cox proportional-hazards survival analysis was performed using "documented contact with adult medical services after age 16 for functional symptoms" as the dependent variable, for the 114 cases over 16 on 31st December 2017. Independent (predictor) variables comprised: explanation model, symptom group, age at presentation, sex, delay to diagnosis, IDACI score (social deprivation index), involvement of clinical psychology at any time and pattern of CAMHS involvement. The results of the model are shown in

Table *3* and Figure 3. High levels of missingness particularly for explanation model (refer to

Table *2*) mean that the model was fitted on only 79 cases. Prior involvement of CAMHS (completed prior to diagnosis of FND) was associated with relapse (HR 3.84; 95%CI 1.25-11.85, $p < 0.05$) in the univariable model but this effect was not retained in the multivariable model. No variables were significantly associated with relapse in the multivariable model (refer to Table 3). .

Discussion

The minimum incidence of FND in childhood is 6 per 100,000 children under 16. This is considerably higher than previous estimates of 1-3 per 100,000[7,8] and comparable to published adult incidence rates[23]. We suggest our higher rates reflect the frequent "mixed picture" situation (also seen in adults[1]) of functional disorder comorbidity alongside coexisting neurological disease, e.g. the combination of non-epileptic seizures with epilepsy. The availability of up to five diagnosis fields in the database from which these cases were ascertained facilitates recognition of such mixed pictures. This may also underlie our finding of a more equal sex distribution than the large excess of females reported in other series[6,7]. Nevertheless, it is important to emphasise that even this figure is very likely to be a severe underestimate of FND rates in children as this is a highly selected population of children reaching specialist paediatric neurology services often because of diagnostic uncertainty in primary and secondary healthcare. Brief, self-limiting symptoms are likely very common in children[6]. We confirm FND rates rise steadily through childhood and adolescence (

Figures

Figure *1*) (the marked reduction in cases over 16 reflects incomplete ascertainment through our paediatric neurology department as in the UK, new presentations in over-16s tend to be seen by adult services). Our youngest presentation at age 4 was three years younger than the youngest recorded by Ani et al.[7] although Kozlowska *et al*'s youngest case was 3[8]. It seems likely that important developmental cognitive milestones (e.g. of self-image[24-26]) make FND more common in older children but are not essential for its occurrence[27].

In up to 21 years' follow up after diagnosis, 26 of the 114 children (23%) who had reached 16 (and who were thus eligible to present to adult services) had documentation of persisting FND of sufficient severity to be recorded in adult medical records. The implied 77% long-term symptom freedom rate is much greater than typically seen in adult-onset FND[9]. We

acknowledge the likelihood of incomplete ascertainment of ongoing FND in adulthood, e.g. if sufferers have become disillusioned about likely medical response to ongoing difficulties and have decided not to seek support. Additionally, since data protection considerations precluded our accessing records of contact with adult mental health services, we cannot identify individuals who are *only* seeing adult mental health services. This view of late outcomes is consistent with a literature suggesting that whilst rates of FND symptom remission may be high in the short term (>75% at 12 months in Ani et al.'s study[7]) the longer term outlook may be poorer[13,14], although still not as bad as adults. Although it is generally assumed that paediatric FND outcomes are better than adult outcomes and that this relates to symptom duration, neither age at presentation nor duration of symptoms prior to diagnosis were associated with long term remission in our results. Adult and paediatric presenters may reflect separate populations with distinct risk factors, although the increased frequency with age of onset suggests overlap [28].

This study has several unique strengths relative to the existing literature on the topic. The available length of follow-up (median 8.3, max 20.8 years from diagnosis of FND) is unprecedented. Although not as large as the UK national surveillance study conducted by Ani et al[7] (*n*=204), our study is also unique in having full access to medical records for details of the pre- and peri-diagnosis periods. We were also able to capture presentations to adult medical specialties other than neurology including the Emergency Department. Limitations inherent in a retrospective casenote review include the lack of standardised measures and data collection protocols. Note that due to the *modus operandi* of the departmental database it is not possible to say much about FND misdiagnosis rates: if in ongoing contact a child initially thought to have FND is subsequently realised to have "organic" neurologic disease the diagnosis fields in the database are updated. The children in this study are thus those for

whom a functional diagnosis has remained in place throughout the period of contact with the paediatric neurology service.

The survival analysis in Table *3* was performed on a subset of the data (79/114) due to high levels of missing data and should be regarded as exploratory in nature only. No reliable predictors of long term remission were identified. Although there is some accumulating evidence for the effectiveness of psychological treatments for paediatric FND[29,30] our data is of limited value in adding to this evidence base. Access to CAMHS support in this series was at clinician discretion, and given CAMHS resource limitations probably reflected recognition of more severe or persistent symptoms. By definition it also implies family willingness to entertain psychological approaches to their child's symptoms. Rates of reported psychological co-morbidity at presentation are low (Table 1) but this may reflect previously-described under-reporting of psychological symptoms in FND[31,32] . Although functional neurological symptoms almost invariably initially present to paediatricians, successful treatment involves collaboration between physical and mental health teams where possible[33]. In a recent survey of 61 Danish paediatricians, only 23% of these practitioners 'often' referred non-epileptic seizures to mental health teams, and 0% 'always' did so[32]. Thankfully our results demonstrate that longterm resolution of symptoms is possible without CAMHS involvement. Effective treatments include rehabilitative[34] and mental health interventions, alongside discouragement of further medical opinion-seeking and investigation.

Paediatric FND is commoner than previous recognised and can have long-term implications. Future research should address the importance of prompt recognition and the role of explanation models in optimising outcomes[32,33,35], particularly as children's understanding will often be mediated through the explanations parents have been given.

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Tables

Table 1. Characteristics of study sample

Characteristic (n= number with data available)	
Interval between initial symptom onset and recognition of functional aetiology (n=124)	Range 0-1866 days; Median 200 days; Inter-quartile range 83-413 days
Coexisting neurological conditions at presentation (n=124)	Active epilepsy 21 Previous epilepsy 5 Active migraine 5 Previous migraine 1 Cerebral palsy 2 Other 5 Nil 85
Coexisting psychological conditions at presentation (n=122)	Anxiety 9 Learning disability 9 Depression 3 ADD + additional features 3 Autism 2 OCD 2 Severe LD 1 Neglect 1 Abnormal illness behaviour 1 Other 2 Nil 89
Other neurological diagnoses considered prior to recognition of FND (n=119)	Epilepsy 24 Other 17 (see text) Migraine 3 Nil 75

Table 2. Classifications of Explanation Model and Parent Acceptance (see text; cases with missing data omitted)

Family response	Fully accepting	Largely accepting	Sceptical	Hostile	Totals
Explanation model					
"All diagnoses excluded"	11	2	2	2	17
Ambiguous	7	5	10	1	23
"Stress-related"	4	1	1	3	9
Explicit naming of FND or equivalent	7	5	2	3	17
Totals	29	13	15	9	66

Table 3. Results of survival analysis. Both the uni- and multivariable models are fitted on data from 79 of the 114 subjects over 16 at 31st December 2017 (missing data precluded fitting on the full sample). Data are right-censored and left-truncated. The dependent 'survival time" variable is the time from sixteenth birthday to the earlier of (i) documented functional symptoms in adulthood or (ii) the study census date of 31 December 2017. Cox proportional hazard model. Hazard ratios are shown with 95% confidence intervals in parentheses and for non-signficiant results are shown to one decimal place[36]. Significance codes: * = p < 0.1; ** = p < 0.05

		HR (univariable)	HR (multivariable)	
Explanation model	"All diagnoses excluded"	-	-	
	Ambiguous	1.6 (0.5, 4.7; p=0.410)	1.6 (0.4, 6.2; p=0.515)	
	Stress related/positive diagnosis of FND	1.2 (0.4, 3.7; p=0.771)	1.3 (0.3, 5.8; p=0.700)	
Symptom group	Seizures	-	-	
	Motor	0.4 (0.1, 1.5; p=0.180)	0.4 (0.1, 2.0; p=0.244)	
	Sensory loss	0.4 (0.1, 1.4; p=0.128)	0.2 (0.04, 1.3; p=0.094)	*
	Pain	0.5 (0.1, 2.2; p=0.365)	0.4 (0.07, 2.2; p=0.293)	
	Other	0.4 (0.1, 1.3; p=0.138)	0.2 (0.03, 1.3; p=0.091)	*
Diagnosis delay	Mean (SD)	1.0 (1.0, 1.0; p=0.814)	1.0 (1.0, 1.0; p=0.485)	
Duration of follow-up in Paediatric Neurology Department	Mean (SD)	1.0 (1.0, 1.0; p=0.417)	1.0 (1.0, 1.0; p=0.928)	
Sex	F	-	-	
	M	0.9 (0.4, 1.9; p=0.693)	0.8 (0.3, 2.7; p=0.749)	
Age	Mean (SD)	1.2 (1.0, 1.4; p=0.100)	1.1 (0.8, 1.4; p=0.633)	
IDACI (socioeconomic deprivation index) score	Mean (SD)	4.1 (0.5, 35.7; p=0.203)	1.3 (0.0, 40.8; p=0.886)	
Early clinical psychology involvement	Yes	-	-	
	No	1.0 (0.5, 2.3; p=0.978)	0.6 (0.2, 1.8; p=0.340)	
Involvement of CAMHS services	No record	-	-	
	after	0.6 (0.2, 1.9; p=0.376)	0.2 (0.0, 1.0; p=0.056)	*
	before	3.84 (1.25, 11.85; p=0.019)**	1.4 (0.2, 12.4; p=0.763)	
	spanning	0.6 (0.2, 1.6; p=0.305)	0.5 (0.1, 2.2; p = 0.356)	

Figures

Figure 1. Distribution of age at presentation and gender

Figure 2 Predominant presenting symptom by age

Figure 3 Survival plot for re-presentation to Adult Medical Services with a diagnosis of FND or equivalent (see text). Small figures above the x axis indicate the diminishing number of remaining cases contributing to the survival data at increasing time after sixteenth birthday.