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The prognosis of functional limb weakness: a 14-year case-control study

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See Edwards (doi:10.1093/brain/awz194) for a scientific commentary on this article.

Reliable data on the prognosis of functional motor disorder are scarce, as existing studies of the prognosis of functional motor disorder are nearly all retrospective, small and uncontrolled. In this study we used a prospectively recruited, controlled cohort design to assess misdiagnosis, mortality and symptomatic and health outcome in patients with functional limb weakness compared to neurological disease and healthy control subjects. We also carried out an exploratory analysis for baseline factors predicting outcome. One hundred and seven patients with functional limb weakness, 46 neurological and 38 healthy control subjects from our previously studied prospective cohort were traced for follow-up after an average of 14 years. Misdiagnosis was determined in a consensus meeting using information from records, patients and their GPs. Numbers and causes of death were collected via death certificates. Outcome of limb weakness, physical and psychiatric symptoms, disability/quality of life and illness perception were recorded with self-rated questionnaires. Outcome measures were compared within and between groups. Seventy-six patients (71%) with functional limb weakness, 31 (67%) neurological and 23 (61%) healthy controls were included in follow-up. Misdiagnosis was found in one patient in the functional limb weakness group (1%) and in one neurological control (2%). Eleven patients with functional limb weakness, eight neurological control subjects and one healthy control subject had died. Weakness had completely remitted in 20% of patients in the functional limb weakness group and in 18% of the neurological controls ($P = 0.785$) and improved in a larger proportion of functional limb weakness patients ($P = 0.011$). Outcomes were comparable between patient groups, and worse than the healthy control group. No baseline factors were independent predictors of outcome, although somatization disorder, general health, pain and total symptoms at baseline were univariably correlated to outcome. This study is the largest and longest follow-up study of functional limb weakness. Misdiagnosis in functional limb weakness is rare after long-term follow-up. The disorder is associated with a higher mortality rate than expected, and symptoms are persistent and disabling. It appears difficult to predict outcome based on common baseline variables. These data should help inform clinicians to provide a more realistic outlook of the outcome and emphasize the importance of active and targeted therapy.

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Introduction

The prognosis of functional motor symptoms is unclear. Whilst there is growing recognition that the diagnosis is normally

stable, there is a notable absence of data to guide clinicians in answering the key question patients ask: ‘will it get better?’

There is now scientific consensus, supported by systematic review, that poorly conducted but widely cited early

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reports of high rates of misdiagnosis were erroneous. Rates of diagnostic revision have been ~4% since 1970 (Stone *et al.*, 2005). But despite this, fears of misdiagnosis are still widely expressed, and some senior clinicians still extol the view that the diagnosis of functional symptoms should not be made for fear of clinical error. Our own large epidemiological study of patients presenting to neurologists with symptoms lacking a pathophysiological explanation, a wider phenotype than functional motor symptoms (Carson *et al.*, 2011), found a much lower frequency of that diagnostic revision and highlighted that actual diagnostic error was rare (4 out of 1040) (Stone *et al.*, 2009). However, follow-up was only 18 months and it could be argued that many alternate diagnoses may only become apparent after the passage of time.

The Scottish Neurological Symptoms Study also had an intriguing secondary finding that a subgroup of patients with dissociative seizures had an unexpectedly high mortality rate of 5% (4 out of 80). This was partially replicated by Duncan *et al.* (2012) who found the premature (<75 years of age) death rate in dissociative seizures was somewhat higher compared to the local national death rate (0.58% compared to 0.41% per year). In functional motor symptoms the limited available data do not provide a meaningful answer (Crimlisk *et al.*, 1998; Deuschl *et al.*, 1998; Feinstein *et al.*, 2001; Stone *et al.*, 2003).

Significantly, more attention has been paid to diagnostic accuracy than patients' actual outcomes. We conducted a systematic review of the prognosis of functional motor symptoms consisting of 24 studies with a duration of follow-up between 1.5 and 12.5 years, with only two longer than 10 years. We found that 39% were the same or worse at follow-up. However, most studies were small, retrospective, performed in tertiary centres, and without a control group. Studies were too heterogeneous for clear predictors to emerge but a long duration between the diagnosis and symptom onset were consistently associated with bad outcome (Gelauff *et al.*, 2014).

In this study we describe the long term follow-up of a prospectively ascertained case-control cohort study of 107 patients with functional limb weakness (Stone *et al.*, 2010, 2012*b*). We aimed: (i) to determine the rate and type of misdiagnosis in the functional limb weakness group and the neurological control group; (ii) to describe the frequency and cause of death in patients with functional limb weakness and compare it to neurological disease and healthy control groups from the same baseline study; (iii) to determine the outcome of limb weakness in terms of change in the presenting symptom, physical and psychiatric symptoms, disability/quality of life and illness perceptions in patients with functional limb weakness compared to neurological controls; and (iv) to conduct an exploratory analysis of baseline factors that predict poor outcome at follow-up in the functional limb weakness group.

Materials and methods

This study received ethical approval from the South Central – Oxford C research ethics committee, a body representing the UK Health Departments' Research Ethics Service (Rec reference: 14/SC/0209). Consent was obtained according to the Declaration of Helsinki.

Baseline

Between 2000 and 2003, 107 patients with functional limb weakness, 46 patients with neurological disorders causing limb weakness (the neurological controls) and 38 healthy subjects (the healthy controls), were included. Patients with functional and neurological limb weakness were recruited consecutively by referral from all consultant neurologists working in South East Scotland (population ~1 million). Inclusion criteria for patients were: weakness/paralysis of one or more limb(s) diagnosed by a consultant neurologist as completely unexplained by organic disease for the functional weakness group, and completely explained by neurological disease in the neurological control group. Symptom onset had to be within the previous 2 years. Patients had to be over 16, able to consent and should not have an intellectual disability. Healthy control subjects, without neurological disease or limb weakness, were asked to take part when they visited their GP for a cervical smear, an oral contraceptive health check or a minor upper respiratory tract infection. Four studies have been published on the baseline data (Stone *et al.*, 2010, 2012*b*; Ludwig *et al.*, 2015; Whitehead *et al.*, 2015).

Follow-up

We located participants from the original study using the electronic record system of NHS Lothian (TRAK) and by contacting GPs (in some cases via Practitioners Services Scotland).

Subjects who agreed to participate provided written informed consent and were then asked to fill out a questionnaire, either online or on paper.

Misdiagnosis

The possibility of misdiagnosis was assessed from three overlapping sources: patients were asked if 'a new diagnosis which explains the weakness at the time of the baseline study' had occurred during follow-up. The patients' GPs were asked the same question by means of a short postal questionnaire. Third, the electronic records system of NHS Lothian was searched to find any indication of misdiagnosis during the follow-up period. Records were classed as 'reviewed' if at least one medical record was available from 2012 onwards.

A consensus meeting (J.S., A.C. and J.G.) was held to review these data and determine whether the initial symptoms of functional or neurological limb weakness could, with the benefit of hindsight, be explained better by another diagnosis. Not all diagnostic revision represents a 'misdiagnosis' and we categorized patients according to the classification of Stone *et al.* (2009).

Deaths

We contacted the National Records of Scotland and England to determine if participants had deceased during the follow-up

period. The primary and secondary cause of death was extracted from death certificates. The UK uses WHO criteria in which the primary cause of death is the disease or event that started the chain of events that led to death, the secondary cause is either a consequence or complication of the primary cause, or another disease, which might have contributed. These were then evaluated against the clinical data from the initial presentation.

Outcome

Outcome in patients and controls was measured by questionnaires. Change in severity of limb weakness in both patient groups was rated on a 6-point Likert scale ranging from ‘completely remitted’ to ‘much worse’. Rates of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS). Overall symptom burden was measured using the current physical symptoms list on the adapted Illness Perceptions Questionnaire (IPQ). Disability/quality of life was assessed using the Medical Outcome Study Short form 36 items (SF36) and the Work and Social Adjustment Scale (WSAS) and questions on whether or not the subject was in work or studying, receiving social and/or health-related benefits. Illness perceptions in patients were measured using selected items from the IPQ (‘My illness is likely to be permanent rather than temporary’, ‘My illness is a mystery to me’, ‘stress or worry was a cause for your weakness’, ‘damage to the nervous system was a cause for your weakness’) scored on a 5-point Likert scale. Patients were asked if they received any treatment, and if so, if this was physiotherapy, psychotherapy and/or any other treatment during the follow-up period. Treatment was not explored further, because patients’ recall of details of treatment was considered biased and unreliable after 12–16 years of follow-up.

Prognostic factors

Several baseline variables were selected for a prognostic factor analysis to predict change in severity of limb weakness [as measured by the Clinical Global Impression (CGI) scale], and for the *post hoc* comparison of patients in follow-up, not in follow-up and deceased, in order to find potential selection bias and predictors of death.

The selection of prognostic baseline variables (Table 4) was based on our systematic review on the prognosis of functional motor disorders (Gelauff *et al.*, 2014), complemented with variables that predicted functional versus neurological limb weakness at baseline (Stone *et al.*, 2010). Prognostic factors were only assessed in the functional weakness group.

Most of these factors were based on standardized questionnaires (Stone *et al.*, 2010). Deprivation category was determined based on postcode data (which is a measure of socioeconomic deprivation), registration of appendectomies and hysterectomies was part of the baseline inventory, as a marker of vulnerability to functional disorders. Change in severity of limb weakness, as measured by the CGI was used as the outcome measure.

Statistical analysis

All patients were analysed in their initial group, irrespective of possible misdiagnosis. Misdiagnosis was reported as a percentage in both patient groups. The standardized mortality

ratio (expected deaths based on national reports/measured deaths) was calculated for both patient groups. The number of people that died in Scotland from 2000 to 2015 was extracted from the National Records of Scotland. As patients were included in our study from 2000 to 2003, standardized mortality ratios for the cohorts from 2000, 2001 and 2002 up and until 2015 were compared to the corresponding cohorts in Scotland separately and a weighted mean standardized mortality ratio was calculated. Baseline characteristics of subjects in follow-up, not in follow-up and the deceased were compared between the three groups using non-parametric testing, in order to find potential selection bias and predictors of death (Chi square, Kruskal-Wallis and Mann-Whitney U-test). Baseline factors that were found to have a prognostic value, were selected *post hoc* for this comparison. No prognostic analyses were performed in patients who had deceased.

Patient outcomes were compared between (follow-up) and within group (follow-up versus baseline). Group comparisons with normally distributed continuous data were tested with *t*-tests (normal or paired for repeated measures). Continuous and categorical data that were not normally distributed were tested using non-parametric methods: Mann-Whitney U- or Chi square tests (between-group analysis), Wilcoxon Signed Rank tests (within-group analysis).

Prognostic factors were determined in the functional weakness group using binary logistic regression analysis. Weakness severity, the dependent variable, was dichotomized into same/worse (bad) or better/remitted (good). Univariate testing was carried out for all baseline factors, all factors that reached a *P*-value < 0.05 were subsequently included in a multivariate analysis. The multivariate binary logistic regression was carried out using backwards elimination.

Additionally, correlations using the non-parametric Spearman’s rho, were made between outcomes and the change from baseline to outcome, to determine if bad outcome of limb weakness is correlated to bad outcome in other domains. Also, correlations were made between improvement of secondary outcome measures and weakness outcome, to determine factors that might be interesting for targeting treatment.

All missing data were reported, no imputation methods were used. To correct for multiple comparisons, we handled interpretation of *P*-values cautiously and considered *P*-values > 0.01 to be insignificant.

Data availability

Data supporting findings can be made available on reasonable request to lead author and subject to appropriate data handling rules. Our original consent procedures from 2000 to 2003 do not allow for individual patient data to be released.

Results

The mean follow-up duration was 14 years for patients with functional limb weakness and neurological control subjects (range 12–16 and 13–15 years, respectively) and 13 years for healthy control subjects (range 12–15 years). Figure 1 shows a flow chart of follow-up, including

misdiagnosis, deaths and patient outcome. Neurological controls that took part in the follow-up study had the following baseline diagnoses: multiple sclerosis ($n = 12$), Guillain-Barré ($n = 4$), transverse myelitis ($n = 3$), clinically isolated syndrome ($n = 1$), ganglionopathy ($n = 1$), ulnar neuropathy ($n = 1$), and myasthenia gravis ($n = 1$). From those who were lost to follow-up, 14 of 19 patients with functional limb weakness, 10 of 11 neurological control subjects and six of seven healthy patients had either definitely or probably moved out of South East Scotland. When patients in follow-up and not in follow-up were compared at baseline (Supplementary Table 1), patients in the functional weakness group who were not in follow-up had a higher percentage of somatization disorder (42% versus 20%, $P = 0.02$). In the neurological control group, patients in follow-up had a significantly worse general health, compared to the group not in follow-up. The healthy control group did not show any differences.

Misdiagnosis

Sufficient data were available to determine whether there had been a change in diagnosis in 85% of the baseline cohort, comprising 89 patients with functional limb weakness and 41 neurological control subjects. The data came from electronic records alone ($n = 49$), and a combination of the patient and/or the GP and/or electronic records ($n = 40$) (Table 1).

In the functional limb weakness group, one patient had a diagnosis of multiple sclerosis, which, with hindsight could have been diagnosed at baseline with the information available at that time. However, it should be noted that this patient still had functional neurological symptoms comorbid to multiple sclerosis symptoms at follow-up. In addition, six patients developed a neurological disorder during the follow-up period that could not explain the initial functional limb weakness. In three of those patients (Huntington's disease, Parkinson's disease and idiopathic cerebellar degeneration), the consensus view was that whilst the disorder would not have directly explained the symptom of functional limb weakness, the prodromal phase of the neurological condition may have contributed to the development of functional weakness. Prodromal phases of neurodegenerative diseases may promote functional disorders for many reasons, including altered somatosensory perception of the limb, or because of alterations in cognition and emotions, especially in relation to attentional processing. In the three cases of ischaemic stroke there were strong reasons to argue the initial functional limb weakness was not related (onset, anatomical location or normal MRI at baseline) and was therefore not considered a transient ischaemic attack or stroke. Finally, for one patient there was uncertainty, at follow-up, whether this patient had a combination of a functional disorder and multiple sclerosis with very limited symptomatology, or only a functional disorder.

In the neurological control group, one patient was categorized as misdiagnosis. The diagnosis of common peroneal palsy was, with the benefit of hindsight, an early sign of spinal muscle atrophy (the stated cause of death in this patient) and therefore labelled as misdiagnosis. One patient developed functional symptoms during follow-up on top of the neurological diagnosis and is therefore categorized as 'de novo' development of 'functional disorder'. Two neurological control subjects with a single episode of demyelination at baseline, developed more episodes, therefore the diagnosis changed to multiple sclerosis. Table 1 summarizes these findings.

Deaths

In 101 patients with functional limb weakness (94%), 45 neurological control subjects (94%) and 30 healthy control subjects (79%) we had sufficient information to determine if they had died during follow-up. Eleven patients with functional limb weakness, eight neurological control subjects and one healthy control subject had died.

The causes of death are shown in Table 2. Within the functional group, the deceased were older at symptom onset, had a worse general health and were in a lower deprivation category at baseline, compared to all other patients with functional limb weakness. No such differences were found within the neurological control group. There was no difference in the number of smokers or opioid users between the deceased group and the other patients at baseline (Supplementary Table 1), although the absolute values of the numbers of smokers were 25% in follow-up compared to 45% in the deceased group, raising the possibility of a type 2 error due to small numbers.

The primary cause of death in the functional limb weakness group were all non-neurological. In three cases the secondary cause of death was a neurological disorder that patients developed after their initial episode of functional weakness; these cases (two with an ischaemic stroke unrelated to initial presentation and one suffering from idiopathic cerebellar degeneration) were discussed above. For two patients no death certificates were available in the UK and we were unable to trace location of death outside of the UK.

In the neurological control group, six out of eight patients' deaths were related to their initial known diagnoses, either as a primary or secondary cause of death [glioblastoma ($n = 2$), multiple sclerosis ($n = 2$), motor neuron disease/spinal muscular atrophy ($n = 2$)].

The (weighted mean) standardized mortality ratio for the death rate under 75 years of age for the functional weakness group was 1.48 and 2.4 for the neurological control group.

Patient outcomes

Table 3 shows all outcome measures at baseline and follow-up for the three groups.

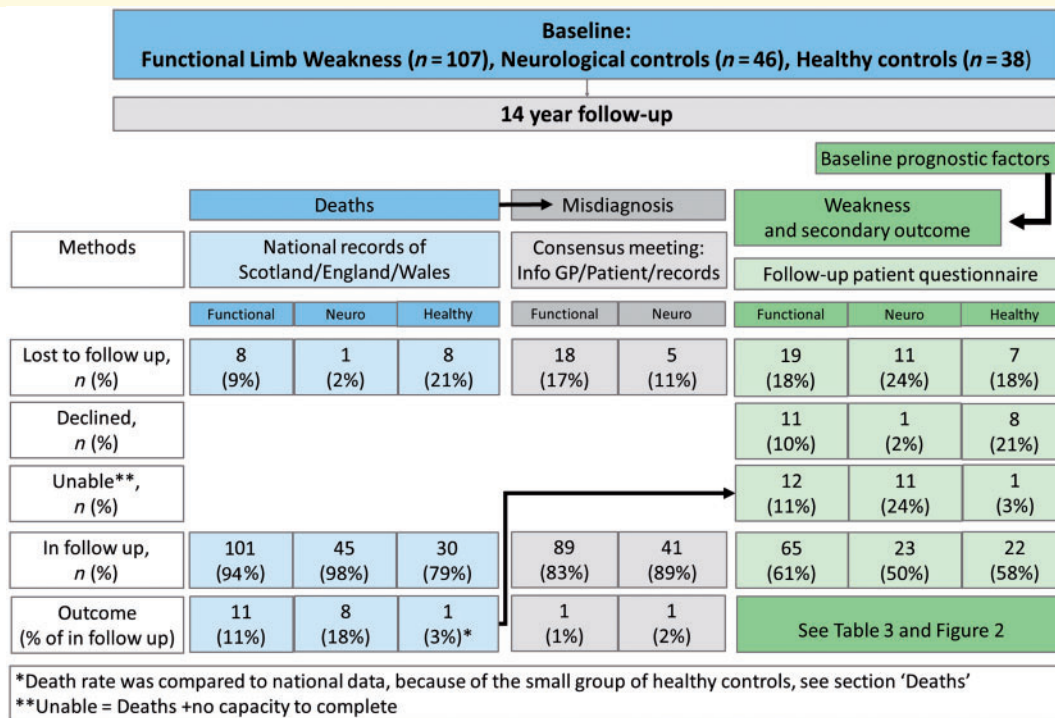


Figure 1 Flow chart follow-up. Misdiagnosis and patient outcome (including deaths) were studied in parallel in the baseline population. Functional = functional limb weakness; Neuro = neurological control subjects; Healthy = healthy control subjects. In eight patients with functional limb weakness, one neurological control subject and eight healthy control subjects we did not have sufficient information to determine if they had died during follow-up. In two of 65 patients with functional limb weakness, only main outcome (acquired by phone) was available.

Table 1 Change in diagnosis during follow-up

Functional limb weakness patients (n = 89)			Neurological controls (n = 41)	
Change of diagnosis category ^a	n	Follow-up diagnosis	n	Follow-up diagnosis
Misdiagnosis	1	Multiple sclerosis and functional disorder	1	Common peroneal nerve palsy changed to spinal muscle atrophy
Diagnostic refinement	-	-	2	Clinically isolated syndrome evolving to multiple sclerosis
De novo development of new disease/disorder	3	Ischaemic stroke	1	New functional disorder in multiple sclerosis patient
Possible prodromal diagnostic change	3	Huntington's disease, Parkinson's disease, Idiopathic cerebellar degeneration	-	-
Disagreement between doctors	1	Disagreement between 'multiple sclerosis and functional disorder' versus only functional disorder	-	-

^aFrom Stone et al. (2009).

Functional limb weakness symptom outcome

Functional limb weakness completely remitted in 20%, improved in 31% (14% much improved, 17% improved) and remained the same or worsened in 49% (23% same, 14% worse, 12% much worse) of patients. In the neurological control group, limb weakness completely remitted in 18%, improved in 8% (4% much improved, 4% improved) and remained the same or worsened in 74% (17% same, 35% worse, 22% much worse). A significantly larger percentage

of patients improved in the functional limb weakness group ($P = 0.011$ on the Mann-Whitney U-test across all categories) but complete remission was equally low in both groups ($P = 0.785$) (Fig. 2).

Depression and anxiety

Depression scores on the HADS were slightly better at follow-up than baseline in the functional limb weakness group, but this did not reach significance (52% at baseline

Table 2 Deceased subjects

	Functional limb weakness (n = 101)		Neurological controls (n = 45)		Healthy controls (n = 30)	Functional versus neuro
Deaths	11 (11%)		8 (18%)		1 (3%)	<i>P</i> = 0.54
Mean age at onset of symptoms (years)	47 (SD 15)		41 (SD 12)		NA	<i>P</i> = 0.310
Mean age at death (years)	56 (SD 14.2)		48 (SD 13.6)		59	<i>P</i> = 0.079
Cause of death	Primary	Secondary	Primary	Secondary	Primary	
Cardiovascular	5	2	-	1	-	-
Malignancy (non-neurological)	1	-	-	-	1	-
Infectious disease	2	1	3	1	-	-
Neurological disorder	-	3	4	2	-	-
Other	1 ^a	-	1	-	-	-
Unknown	2	-	-	-	-	-
Death related to initial presentation with limb weakness	None	-	6 (75%)	-	-	-
Standardized mortality ratio (weighted mean)	1.48	-	2.4	-	-	-

Based on data of 176 out of 191 baseline subjects (92%). Comparison of age: Mann Whitney U-test, comparison of number of deaths: Chi square test. Causes of death (both primary and secondary) are given as stated on the death certificate. Secondary neurological disorders in the functional group were idiopathic cerebellar degeneration and ischaemic stroke (*n* = 2).

^aCause of death: systemic sclerosis.

SD = standard deviation.

versus 37% at follow-up, above the cut-off of 8; *P* = 0.137). In the neurological control group, percentage of patients above the cut-off of 8, decreased from 41% to 27% (*P* = 0.508), with no statistical difference. In the healthy control subjects, numbers changed from 32% to 11% (*P* = 0.219). Follow-up depression scores in the functional limb weakness group were not statistically different from the neurological control group (*P* = 0.616) and scores were worse than the healthy control group (*P* = 0.037).

Mean anxiety levels on the HADS were comparable in the three groups at follow-up, using a cut-off score >8, 69% of functional weakness patients, 36% of neurological controls and 42% of healthy controls suffered from anxiety, which was not statistically different.

Global symptom burden

Compared to baseline, we did not find a change in the number of co-morbid symptoms, measured on the IPQ symptom list, in patients with a functional disorder [baseline median 9, interquartile range (IQR) 4, follow-up median 8, IQR 5; *P* = 0.076] or neurological controls (baseline median 8, IQR 3, follow-up median 7, IQR 5; *P* = 0.986), nor a difference between patient groups at follow-up (*P* = 0.292). In healthy control subjects, only data at follow-up were available (median 3, IQR 4). They scored significantly lower than the functional limb weakness group (*P* < 0.001).

Disability/quality of life

At follow-up, 54% of the functional limb weakness patients reported fair or poor general health compared to 39% in the neurological control group (*P* = 0.122) and 9% in the healthy control group (*P* < 0.001). In none of

the groups was there a significant change compared to baseline. Patients with functional limb weakness and neurological control subjects scored similarly on all subdomains of the health-related quality of life and functioning SF36 scale at follow-up, except for pain, which was worse in the functional limb weakness group (*P* = 0.018). The functional limb weakness group scored significantly worse on almost all of these domains (physical functioning, physical role functioning, energy, pain) compared to the healthy control group, except for the emotional role functioning domain and the social functioning domain.

At follow-up in the functional limb weakness group, 41% were not employed for health-related reasons. In comparison, 39% versus 9% were out of work for health-related reasons in the neurological and healthy control groups, respectively. The work and social adjustment scale showed similar outcomes in functional and neurological groups, while healthy controls were much less impaired. As at baseline, there was no statistical difference in the number of patients in receipt of state-related financial benefits at follow-up between functional and neurological groups (43% versus 65%, *P* = 0.066).

Illness perception

At baseline, 89% of patients with functional limb weakness agreed or strongly agreed that the limb weakness they experienced was a mystery to them, while at follow-up this was 51% (*P* < 0.001). At baseline, 23% of patients agreed stress or worry was a causative factor for their limb weakness, versus 19% at follow-up (*P* = 0.695) and for damage to the nervous system the percentages were 31% at baseline and 32% at follow-up (*P* = 0.186), suggesting remarkable stability of illness beliefs.

Table 3 Outcome measures in patients and controls

	Functional weakness (n in follow-up = 63)		Neurological controls (n in follow-up = 23)		Healthy controls (n in follow-up = 22)		Functional weakness versus neuro controls follow-up	Functional weakness versus healthy controls follow-up
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up		
Depression and anxiety (HADS), % > cut-off score of 8								
Depression	52%	37%	41%	27%	32%	11%	P = 0.219 ^b	P = 0.616 ^c
Anxiety	47%	69%	14%	36%	11%	42%	P = 0.031 ^b	P = 0.226 ^c
Physical symptoms (IPQ plus 5 neurological symptoms)								
Symptom list, median (IQR)	9 (4)	8 (5)	8 (3)	7(5)	NA	3 (4)	-	P = 0.292
Health-related quality of life and functioning (SF36)^a								
General health, % fair/poor ^e	42%	54%	14%	39%	11%	9%	P = 0.179 ^d	P = 0.122 ^e
Physical functioning, median (IQR)	35 (49)	55 (70)	45 (65)	30 (75)	95 (10)	90 (16.25)	P = 0.113 ^d	P = 0.487 ^e
Role physical, median (IQR)	0 (19)	0 (100)	13 (75)	25 (75)	100 (0)	100 (100)	P = 0.269 ^d	P = 0.912 ^e
Role emotional, median (IQR)	33 (100)	100 (100)	100 (42)	100 (100)	100 (0)	100 (100)	P = 0.931 ^d	P = 0.777 ^e
Energy, median (IQR)	25 (40)	40 (40)	33 (36)	33 (53)	50 (15)	70 (27)	P = 0.002 ^d	P = 0.930 ^e
Pain, median (IQR)	33 (35)	20 (20)	50 (24)	20 (20)	50 (40)	40 (20)	P = 0.007 ^d	P = 0.018 ^e
Social functioning, median (IQR)	44 (38)	50 (25)	50 (53)	50 (12.5)	50 (25)	50 (12.5)	P = 0.015 ^d	P = 0.193
Work, social adjustment and benefits								
WSAS score, median (IQR)	NA	17 (27)	-	18 (19)	-	0 (8.75)	-	P = 0.868 ^e
In paid employment	34%	40%	70%	39%	95%	68%		
Unemployed health related	62%	41%	22%	39%	0%	9%	P = 0.012 ^d	P = 0.960 ^c
Any benefits	49%	43%	30%	65%	4.5%	9%	P = 1.00 ^b	P = 0.066 ^c

SF36 functioning and disability scale (range 0–100): high score means better functioning or less pain. Work and social adjustment scale (range 0–40): higher score means worse impairment. HADS = Hospital Anxiety and Depression Scale; IPQ = Illness Perceptions Questionnaire; WSAS = Work and Social Adjustment Scale.

^aData on the SF36 general health question were available in 65 functional patients (instead of 63). Missing data: SF36 and HADS baseline data in one functional weakness patient, one neurological control and three healthy controls.

^bMcNemar statistical analysis (for binominal data).

^cChi-square test.

^dWilcoxon signed rank.

^eMann-Whitney U-test.

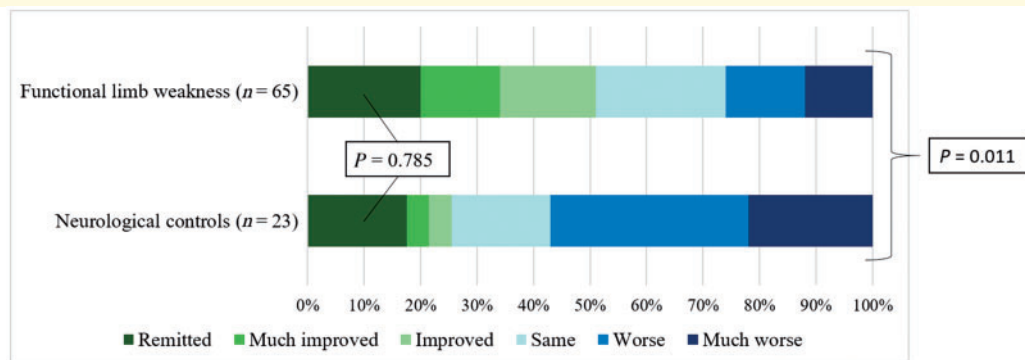


Figure 2 The severity of limb weakness at follow-up in the functional limb weakness group and the neurological control group. A Mann-Whitney U-test comparing the whole scale in both groups, provided a P -value of 0.011.

Treatment

Fifty-two per cent of patients with functional limb weakness versus 70% of neurological control subjects ($P = 0.154$) reported receiving some form of treatment for their limb weakness during the follow-up period. Of the patients with functional weakness, 76% reported receiving physiotherapy at some stage during the follow-up period, and 36% reported receiving psychotherapy. In the neurological control group, 75% reported physiotherapy, and only one patient reported psychotherapy. Other therapies in the neurological control group included medication for the underlying condition.

Prognostic factors and correlations

Univariate analysis of prognostic factors in the functional limb weakness group is shown in Table 4. Patients with baseline presence of somatization disorder [0.22 (0.05–0.89) $P = 0.034$], pain [1.04 (1.01–1.06) $P = 0.007$] and a high number of physical symptoms [0.84 (0.72–0.19 = 0) $P = 0.037$] were less likely to improve. Patients with a better general health score on the SF36 at baseline [1.03 (1.00–1.05) $P = 0.017$] were more likely to improve. The multivariate analysis showed none of the factors alone significantly predicted weakness outcome. This multivariate model provided a Cox and Snell R^2 of 0.17, suggesting that these factors were only explaining a small amount of the variance.

In the functional weakness group, several follow-up outcome measures: general health, physical functioning, pain, energy, work and social adjustment and the total number of symptoms on the IPQ symptom list, showed significant correlations with weakness severity at follow-up (Supplementary Table 2). Depression and anxiety did not correlate with weakness outcome. In the neurological group this was only the case for physical functioning. Change in energy correlated only weakly to a change in weakness severity in the functional group ($\rho = -0.361$ $P = 0.004$). In the neurological group, a change in physical functioning correlated strongly to change in weakness severity (ρ

-0.712 , $P < 0.001$), and change in pain correlated moderately to a change in weakness severity ($\rho = -0.610$, $P = 0.003$). Any treatment during the follow-up period did not influence weakness severity outcome in both groups.

Discussion

This study is the largest and longest prospectively recruited follow-up study of functional limb weakness, and also includes a neurological and healthy control group. It is also the longest follow-up study ever for any functional neurological disorder (Gelauff and Stone, 2016).

Misdiagnosis

In this study, we found only one example of clear-cut misdiagnosis of functional limb weakness (1/89 = 1%), which was half the misdiagnosis rate of the neurological control group (1/41 = 2%). In three additional patients the development of functional limb weakness may have been part of a non-specific prodrome to the development of a neurodegenerative condition not associated with limb weakness. This is in line with observations that functional neurological disorders often occur in the context of recognized neurological disease (Stone *et al.*, 2012a; Pareés *et al.*, 2013; Wissel *et al.*, 2018).

Even accounting for these possible prodromal cases, the misdiagnosis rate was low, and in keeping with other recent studies of functional neurological disorders, as discussed in the introduction. Our prospectively ascertained follow-up data were acquired over a much longer time period than any other study and provide important evidence of the stability and persistence of the symptoms in patients with functional limb weakness. These findings should encourage physicians to consider misdiagnosis in this patient population no more of an issue than in other neurological conditions. Reluctance to make a positive diagnosis of a functional motor disorder, or diagnostic uncertainty can powerfully impair treatment. We recommend

Table 4 Prognostic factors

Baseline variables	Limb weakness severity (CPS)			
	Univariate analysis		Multivariate analysis	
	Odds ratio (CI 95%)	P-value	Odds ratio (CI 95%)	P-value
Age at onset	1.01 (0.96–1.05)	0.829	–	–
Gender	1.25 (0.30–5.15)	0.757	–	–
Symptom duration	0.98 (0.92–1.04)	0.474	–	–
Being in work	1.13 (0.81–1.57)	0.486	–	–
Benefits	0.43 (0.16–1.18)	0.100	–	–
Deprivation category	0.64 (0.41–1.00)	0.050	–	–
Appendectomy	0.70 (0.24–2.10)	0.528	–	–
Hysterectomy	0.30 (0.08–1.10)	0.069	–	–
Psychiatric co-morbidity and childhood trauma				
Depression (HADS)	0.99 (0.90–1.08)	0.769	–	–
Anxiety (HADS)	0.95 (0.86–1.04)	0.273	–	–
Somatization disorder (SCID)	0.22 (0.05–0.89)	0.034	0.44 (0.09–2.14)	0.312
Total psychiatric diagnoses on SCID	0.81 (0.58–1.13)	0.210	–	–
Physical abuse (CTQ)	1.00 (0.89–1.13)	1.000	–	–
Sexual abuse (CTQ)	1.02 (0.93–1.12)	0.723	–	–
Health-related quality of life and functioning (SF36)				
General health	1.03 (1.00–1.05)	0.017	1.02 (1.00–1.04)	0.085
Physical functioning	1.02 (1.00–1.03)	0.065	–	–
Pain	1.04 (1.01–1.06)	0.007	1.03 (1.00–1.06)	0.030
Energy	1.01 (0.99–1.04)	0.268	–	–
Illness perception (IPQ)				
'my weakness is a mystery to me'	1.08 (0.57–2.05)	0.808	–	–
'my weakness is permanent rather than temporary'	0.82 (0.55–1.22)	0.330	–	–
'what I do can determine if my illness gets better or worse'	1.23 (0.77–1.96)	0.392	–	–
'damage to nervous system caused my symptoms'	1.12 (0.70–1.80)	0.628	–	–
'stress or worry caused my symptoms'	1.14 (0.78–1.67)	0.487	–	–
'I wish the doctor had listened more'	0.83 (0.54–1.24)	0.353	–	–
'I have lost faith generally in doctors'	0.96 (0.67–1.36)	0.804	–	–
IPQ number of symptoms	0.84 (0.72–0.99)	0.037	0.93 (0.78–1.10)	0.375

Univariate and multivariate binary logistic regression analysis of baseline factors on two dichotomized outcome measures. For both outcome measures, the relationship of baseline factors with good outcome is displayed. R^2 (Cox and Snell) 0.17.

CPS = Change in Presenting Symptoms Scale; CTQ = Childhood Trauma Questionnaire; HADS = Hospital Anxiety and Depression Questionnaire; IPQ = Illness Perceptions Questionnaire; SCID = Structured Clinical Interview for DSM.

that physicians should continue to reconsider any neurological diagnosis and remain vigilant of co-morbid neurological disease, which is a powerful risk factor for all functional disorders. Our findings create an argument for neurologists to stay involved with the long-term management of at least some patients with functional limb weakness, to guide treatment and detect neurological disease, sometimes occurring years after the functional symptoms start.

Deaths

In our cohort, we found a standardized mortality ratio for the death rate under 75 years of age for the functional weakness group of 1.48 and of 2.4 for the neurological control group. Duncan *et al.* (2014) found a death rate of 0.58% per year in a group of patients with psychogenic non-epileptic attacks ($n = 260$). This was somewhat lower than our findings (our data converted to death rates:

0.77% per year in functional limb weakness and 1.27% in neurological controls). In that study, as in ours, none of the causes of death were directly related to the initial symptoms. Cardiovascular cause of death was most frequent. There are very limited data on death rates from other follow-up studies in functional motor symptoms. From two studies in functional weakness, one patient out of 56 died after 12 years follow-up (Stone *et al.*, 2003), and 5 of 64 after 5–7 years of follow-up (Crimlisk *et al.*, 1998). In the latter, one patient died of pneumonia due to immobilization (in a tetraplegic patient), one died of possible overdose, the others in these two studies died of cardiovascular disease or malignancy. These findings correspond generally to our findings. In two retrospective studies in movement disorders, 1 of 25 (Deuschl *et al.*, 1998) and 3 of 88 (Feinstein *et al.*, 2001) died, one from suicide and the others of unrelated causes. The increased death rate in our cohort compared to the general population may have several causes: (i) three patients died of neurodegenerative

diseases, and their functional limb weakness may have been part of a prodromal state; (ii) secondary effects of having chronic illness including depression, anxiety or stress where present; (iii) among patients with functional weakness patients, those that died had a poorer general health status at baseline compared to the patients that survived; and (iv) it is possible that patients with functional weakness had a more sedentary lifestyle, because the cause of death was often cardiovascular and a lower deprivation category was associated with death. However other cardiovascular factors were not found to be increased in the deceased group, although numbers were small, so caution is due for type 2 error.

Patient outcomes

In 80% of the functional limb weakness group, patients still had symptoms of weakness in one or more limb(s) after an average of 14 years follow-up, compared to 83% of patients in the neurological control group. There was a similar remission rate but overall better prognosis in the functional group compared to the neurological controls. The results are in line with our earlier retrospective follow-up study in which 83% of 42 patients still had weakness after 12.5 years (Stone *et al.*, 2003). Other smaller studies of outcome of patients with functional weakness, with 10–30 patients over 0.5–6 years, found a large range of outcomes with 10–56% being the same or worse weakness at follow-up (Carter, 1949; Brown and Pisetsky, 1954; Knutsson and Mårtensson, 1985; Binzer and Kullgren, 1998).

From a scientific perspective, it would be useful to investigate the natural history of untreated patients with functional limb weakness. Inevitably a large percentage of patients received some form of treatment (52% in the functional weakness group, 70% of neurological controls) during follow-up. Treatment did not correlate to outcome. However, the nature of these treatments remained unclear, as our study was not focused on treatment, and the reported treatments were not standardized or randomized. Also, we could not reliably collect data on types of treatment using self-report over a period of 14 years. One of the authors (J.S.) saw all the patients for research assessments at baseline between 2000 and 2003, not for specific treatment. Patients were told they were in a study of ‘unexplained motor symptoms’ only and did not receive the detailed explanations, supported by written materials, that they would in Edinburgh in 2019. The impression from review was that it was often not delivered by practitioners experienced in functional disorders.

Mirroring the persistent nature of the symptom of functional limb weakness, patients also failed to improve on most secondary health outcome measures. Total symptom burden and measures of disability/quality of life were all correlated moderately to weakness severity, which (with the exception of physical functioning) were not found in the neurological control group. This could be due to quality of

life being more greatly determined by functional symptoms in the functional weakness group compared to neurological controls.

More patients with functional limb weakness were out of work at follow-up than had been at baseline. Other studies of patients with functional motor disorders have found a low frequency of being in work ranging from 11% to 57% (Binzer and Kullgren, 1998; Crimlisk *et al.*, 1998). In our data, patients with functional weakness were less likely to receive benefits at follow-up (43%) than neurological controls (65%), although this did not reach significance ($P = 0.066$), while disability at follow-up was equal. In contrast to findings from the Scottish Neurological Symptoms Study of 3781 outpatients (Carson *et al.*, 2011), in which patients with functional disorders in general were slightly more likely to be on disability benefits, receipt of benefits did not predict outcome in patients with functional limb weakness.

Over time, financial benefits for patients with functional limb weakness did not increase and receiving benefits did not predict outcome, which contradicts the notion that patients would perpetuate their symptoms in order to gain benefits.

Prognostic factors

Several factors were found to influence weakness severity at follow-up in the univariate analysis. General health at baseline was, perhaps unsurprisingly, found to be associated with limb weakness outcome. Pain was also found to influence symptom outcome. From clinical practice we know pain is an important impairing symptom for many patients with functional limb weakness. However it has only been studied in fixed dystonia, where it was found to be a negative predictor (Ibrahim *et al.*, 2009). In our limb weakness study, many patients had low pain scores at baseline [median score 33 out of 100, (IQR 35), lower score equates to more pain], and even worse (median 20, IQR 20, $P < 0.001$) at follow-up, which was significantly worse than the control groups. Also, a change in pain between baseline and follow-up was correlated to general health outcome. This highlights the importance of assessing pain at baseline and possibly targeting it as a stratifying factor in treatment trials.

Somatization disorder at baseline, an indicator of individuals with functional symptoms in several domains, was also found to influence limb weakness at follow-up negatively in univariate analysis. In total, 13 patients met the criteria for somatization disorder at baseline. Of those, 12 (92%) had poor or fair general health and 10 (77%) had same or worse weakness at follow-up. The two studies that have investigated this have found no correlation between somatoform disorders and outcome (Crimlisk *et al.*, 1998; Ibrahim *et al.*, 2009). From our data, patients with a long-standing vulnerability to various symptoms throughout their life, do seem to have a worse prognosis. Total number of physical symptoms at baseline, which was also

found to be a univariate prognostic factor, could be seen in the same light.

The factors we included in the prognostic analysis were determined based on previous findings in the literature and in our baseline study, but many factors were not found to have a prognostic value. For age and gender, this was expected based on the literature. It was however striking that factors found to be predictive in other studies like benefits, working status, frequency of physical and sexual abuse and certain illness perceptions, were not prognostic (Gelauff *et al.*, 2014). Notwithstanding the risk of a false negative result, as our numbers are relatively low for a multivariate analysis, these are important observations, as many of these factors are often suggested to play an important role in the prognosis of functional neurological disorders.

Factors that have most consistently correlated with positive outcome in the literature included an early diagnosis and short duration of symptoms at baseline (Knutsson and Mårtensson, 1985; Couprie *et al.*, 1995; Factor *et al.*, 1995; Mace and Trimble, 1996; Crimlisk *et al.*, 1998; Feinstein *et al.*, 2001; Thomas *et al.*, 2006; Jankovic *et al.*, 2006; McKeon *et al.*, 2009; Munhoz *et al.*, 2011; Erro *et al.*, 2014). Symptom duration before diagnosis was not found to be a prognostic factor in our study. However, the original study set a maximum 2 years of symptom duration as an inclusion criterion at baseline, which means this study could not easily investigate that issue.

Generally, we found it difficult to predict outcome in our cohort, let alone at a patient level. Apart from the low yield of prognostic factors, part of the problem may be heterogeneity between patients. Moreover, our model only explained 17% of the variance of the functional weakness outcome, and 38% of the general health outcome, which means other unknown factors influence outcome substantially. In practice, this means that clinicians should be wary about judging the likely outcome in individuals with functional limb weakness and keep an open mind, regardless of apparently poor prognostic features.

Limitations

Inclusion in the original study was consecutively by all neurologists working in a regional clinical neurosciences centre covering the South-east Scotland region, population about one million. Our sample is likely to be representative of the population in this region, as there are very limited alternative neurological services in the area (limited private care and no inpatient private neurological beds). Incomplete ascertainment at follow-up is clearly a potential issue. However, our follow-up rate of 71% in the functional weakness group after 14 years (including the deceased patients) is respectable given the duration of time, and baseline variables appeared similar between responders and non-responders. There was a higher percentage of patients with functional weakness in the group not in follow-up with somatization disorder (42%) compared to the group in follow-up (20%). As we found somatization

disorder to be a (univariable) predictor of bad outcome, the higher dropout of these patients could have caused bias towards a more favourable outcome. Patients who could not be contacted had most commonly moved out of the area, so are arguably less likely to be a confounding factor. Patients declining to participate most likely introduced confounding; however, whether that would be in favour of good or bad outcome is speculative. Our results on misdiagnosis may have been biased by the fact that these patients were all part of a study. Patients in whom there was doubt about the diagnosis may have been less likely to be referred to the study. Our data on cause of death are partly limited by accuracy of death certification. The patient outcome data were based on self-report. However, in previous studies comparing subjective and objective outcome measures, there has been little difference between the two. Patients with very short duration of symptoms were not included in this study (i.e. if they had recovered by the time of the baseline assessment). As duration of symptoms has been found to be a negative prognostic factor (Gelauff *et al.*, 2014), prognosis may be better in patients presenting to primary care or emergency settings.

Conclusion

Functional limb weakness can be diagnosed accurately, and misdiagnosis is rare even after long-term follow-up. Functional limb weakness is persistent, disabling, and associated with higher mortality than expected. It is very difficult to predict outcome based on common baseline variables, although pain and propensity to longstanding multiple functional disorders may be important stratifying variables for clinical trials and treatment decision-making. These data should help clinicians to provide a more realistic prognosis for functional weakness patients and also stress the importance of active and targeted treatment.

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Competing interests

A.C. gave independent testimony in court on a range of neuropsychiatric disorders (50% pursuer:50% defender) and was paid associate editor of the *Journal of Neurology, Neurosurgery and Psychiatry*. The remaining authors did not report competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

- Binzer M, Kullgren G. Motor conversion disorder. A prospective 2- to 5-year follow-up study. *Psychosomatics* 1998; 39: 519–27.
- Brown W, Pisetsky J. Sociopsychologic factors in hysterical paraplegia. *J Nerv Ment Dis* 1954; 119: 283–98.
- Carson A, Stone J, Hibberd C, Murray G, Duncan R, Coleman R, et al. Disability, distress and unemployment in neurology outpatients with symptoms ‘unexplained by organic disease’. *J. Neurol. Neurosurg. Psychiatry* 2011; 82: 810–3.
- Carter a B. The prognosis of certain hysterical symptoms. *Br Med J* 1949; 1: 1076–9.
- Couprie W, Wijdicks EF, Rooijmans HG, van Gijn J. Outcome in conversion disorder: a follow up study. *J Neurol Neurosurg Psychiatry* 1995; 58: 750–2.
- Crimlisk HL, Bhatia K, Cope H, David A, Marsden CD, Ron M a. Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms. *BMJ* 1998; 316: 582–586.
- Deuschl G, Koster B, Lucking CH, Scheidt C. Diagnostic and pathophysiological aspects of psychogenic tremors. *Mov Disord* 1998; 13: 294–302.
- Duncan R, Graham CD, Oto M. Outcome at 5–10years in psychogenic nonepileptic seizures: What patients report vs. what family doctors report. *Epilepsy Behav* 2014; 37: 71–4.
- Duncan R, Oto M, Wainman-Lefley J. Mortality in a cohort of patients with psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry* 2012; 83: 761–2.
- Erro R, Edwards MJ, Bhatia KP, Esposito M, Farmer SF, Cordivari C. Psychogenic axial myoclonus: Clinical features and long-term outcome. *Park Relat Disord* 2014; 20: 596–9.
- Factor SA, Podskalny GD, Molho ES. Psychogenic movement disorders: frequency, clinical profile, and characteristics. *J Neurol Neurosurg Psychiatry* 1995; 95: 406–12.
- Feinstein a, Stergiopoulos V, Fine J, Lang a E. Psychiatric outcome in patients with a psychogenic movement disorder: a prospective study. *Neuropsychiatry Neuropsychol Behav Neurol* 2001; 14: 169–76.
- Gelauff J, Stone J. Prognosis of functional neurologic disorders. In: *Handbook of Clinical Neurology*; 2016. p. 523–41.
- Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. *J Neurol Neurosurg Psychiatry* 2014; 85: 220–6.
- Ibrahim NM, Martino D, van de Warrenburg BPC, Quinn NP, Bhatia KP, Brown RJ, et al. The prognosis of fixed dystonia: a follow-up study. *Park Relat Disord* 2009; 15: 592–7.
- Jankovic J, Vuong KD, Thomas M. Psychogenic tremor: long-term outcome. *CNZ Spectr* 2006; 11: 501–8.
- Knutsson E, Mårtensson A. Isokinetic measurements of muscle strength in hysterical paresis. *Electroencephalogr. Clin Neurophysiol* 1985; 61: 370–4.
- Ludwig L, Whitehead K, Sharpe M, Reuber M, Stone J. Differences in illness perceptions between patients with non-epileptic seizures and functional limb weakness. *J Psychosom Res* 2015; 79: 246–9.
- Mace CJ, Trimble MR. Ten-year prognosis of conversion disorder. *Br J Psychiatry* 1996; 169: 282–8.
- McKeon A, Ahlskog JE, Bower JH, Josephs KA, Matsumoto JY. Psychogenic tremor: long-term prognosis in patients with electrophysiologically confirmed disease. *Mov Disord* 2009; 24: 72–76.
- Munhoz RP, Zavala JA., Becker N, Teive HAG. Cross-cultural influences on psychogenic movement disorders - a comparative review with a Brazilian series of 83 cases. *Clin Neurol Neurosurg* 2011; 113: 115–8.
- Pareés I, Saifee TA, Kojovic M, Kassavetis P, Rubio-Agusti I, Sadnicka A, et al. Functional (psychogenic) symptoms in Parkinson’s disease. *Mov Disord* 2013; 28: 1622–7.
- Stone J, Carson a., Duncan R, Coleman R, Roberts R, Warlow C, et al. Symptoms ‘unexplained by organic disease’ in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? *Brain* 2009; 132: 2878–88.
- Stone J, Carson A, Duncan R, Roberts R, Coleman R, Warlow C, et al. Which neurological diseases are most likely to be associated with ‘symptoms unexplained by organic disease’. *J. Neurol* 2012a; 259: 33–8.
- Stone J, Sharpe M, Rothwell PM, Warlow CP. The 12 year prognosis of unilateral functional weakness and sensory disturbance. *J Neurol Neurosurg Psychiatry* 2003; 74: 591–6.
- Stone J, Smyth R, Carson A, Lewis S, Prescott R, Warlow C, et al. Systematic review of misdiagnosis of conversion symptoms and ‘hysteria’. *BMJ* 2005; 331: 989.
- Stone J, Warlow C, Sharpe M. The symptom of functional weakness: a controlled study of 107 patients. *Brain* 2010; 133: 1537–51.
- Stone J, Warlow C, Sharpe M. Functional weakness: clues to mechanism from the nature of onset. *J. Neurol Neurosurg Psychiatry* 2012b; 83: 67–9.
- Thomas M, Vuong KD, Jankovic J. Long-term prognosis of patients with psychogenic movement disorders. *Park Relat Disord* 2006; 12: 382–7.
- Whitehead K, Stone J, Norman P, Sharpe M, Reuber M. Differences in relatives’ and patients’ illness perceptions in functional neurological symptom disorders compared with neurological diseases. *Epilepsy Behav* 2015; 42: 159–64.
- Wissel BD, Dwivedi AK, Merola A, Chin D, Jacob C, Duker AP, et al. Functional neurological disorders in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2018; 89: 566–71.