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Symptoms 'unexplained by organic disease' in 1144 new neurology out-patients: how often does the diagnosis change at follow-up?

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It has been previously reported that a substantial proportion of newly referred neurology out-patients have symptoms that are considered by the assessing neurologist as unexplained by 'organic disease'. There has however been much controversy about how often such patients subsequently develop a disease diagnosis that, with hindsight, would have explained the symptoms. We aimed to determine in a large sample of new neurology out-patients: (i) what proportion are assessed as having symptoms unexplained by disease and the diagnoses given to them; and (ii) how often a neurological disorder emerged which, with hindsight, explained the original symptoms. We carried out a prospective cohort study of patients referred from primary care to National Health Service neurology clinics in Scotland, UK. Measures were: (i) the proportion of patients with symptoms rated by the assessing neurologist as 'not at all' or only 'somewhat explained' by 'organic disease' and the neurological diagnoses recorded at initial assessment; and (ii) the frequency of unexpected new diagnoses made over the following 18 months (according to the primary-care physician). One thousand four hundred and forty-four patients (30% of all new patients) were rated as having symptoms 'not at all' or only 'somewhat explained' by 'organic disease'. The most common categories of diagnosis were: (i) organic neurological disease but with symptoms unexplained by it (26%); (ii) headache disorders (26%); and (iii) conversion symptoms (motor, sensory or non-epileptic attacks) (18%). At follow-up only 4 out of 1030 patients (0.4%) had acquired an organic disease diagnosis that was unexpected at initial assessment and plausibly the cause of the patients' original symptoms. Eight patients had died at follow-up; five of whom had initial diagnoses of non-epileptic attacks. Seven other types

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of diagnostic change with very different implications to a 'missed diagnosis' were found and a new classification of diagnostic revision is presented. One-third of new neurology out-patients are assessed as having symptoms 'unexplained by organic disease'. A new diagnosis, which with hindsight explained the original symptoms, rarely became apparent to the patient's primary care doctor in the 18 months following the initial hospital consultation.

Keywords: conversion disorder; neurology; medically unexplained symptoms; misdiagnosis; prognosis

Introduction

There is a growing recognition that the symptoms patients present to doctors with are often not associated with the presence of an 'organic disease'. Indeed, studies from the UK, Holland and Denmark have all reported that around one-third of new patients seen in neurology clinics have symptoms that are judged to be either not at all, or only partly, explained by organic disease (Carson *et al*., 2000*b*; Nimnuan *et al*., 2001; Stone *et al*., 2002, 2004; Snijders *et al*., 2004; Fink *et al*., 2005).

However, for many doctors and patients a critical and controversial question remains: how often do these apparently 'unexplained' symptoms later turn out to have been due to organic disease? A frequently cited article by Eliot Slater, published in 1965, suggested that as many as 60% of patients who were diagnosed with 'hysteria' developed 'organic' disease at subsequent follow-up (Slater, 1965). Nearly half a century later, Slater's warning is remembered by many and continues to influence modern clinical practice by making some neurologists reluctant to assess symptoms as unexplained by 'organic disease'. Our own systematic review of follow-up studies of patients with conversion symptoms and 'hysteria' found that the development of organic disease occurred in only 4% of patients in follow-up studies published since 1970 (Stone *et al*., 2005). However, our confidence in this conclusion was limited by the quality of the studies reviewed, which were mostly small, single centre, retrospective, involving mainly in-patients and often of poor quality.

We therefore aimed to determine, in a large representative sample of new neurology out-patients: (i) what proportions have symptoms that the neurologist considers that are unexplained by organic disease; (ii) the initial diagnoses given to these patients by the assessing neurologists; and (iii) over the following 18 months, how many acquire a new diagnosis of organic disease which, with hindsight, could have explained the original symptoms.

Material and Methods

The Scottish Neurological Symptoms Study was a prospective, multi-centre cohort study of neurology out-patient practice in the National Health Service (NHS) in Scotland UK (population 5 057 400 at the time of the study). Ethical approval for the study was granted by a multi-centre research ethics committee.

Participating clinics

In total 36 out of 38 consultant neurologists participated, working across all four Scottish NHS neurology centres. Patients were recruited from their general neurology clinics (including their supervised trainee clinics) in the main Scottish neurological centres—Aberdeen, Dundee, Edinburgh and Glasgow and eight associated peripheral clinics, from December 2002 to February 2004. All the clinics sampled took mainly primary care referrals. Tertiary clinics, where patients required a verified diagnosis to attend (such as acute neurovascular and multiple sclerosis clinics) were excluded as were 'urgent case' emergency clinics.

Patients

All patients newly referred to the participating neurology out-patient clinics were potentially eligible for inclusion. However, we excluded those who were: aged less than 16, had cognitive or physical impairment of a degree that precluded informed consent, were unable to read English or regarded by the neurologist as unsuitable for the study (e.g. too distressed, terminally ill). Patients were sent information about the study prior to their appointment with the neurologist. After the consultation they were invited by their neurologist to speak to a research assistant and consent was obtained from those willing to participate.

Measures

Baseline information

Immediately after the initial consultation the participating neurologists rated each patient with regard to the following question: *'To what extent do you think this patient's clinical symptoms are explained by organic disease?'* on a four-point Likert-type scale as *'not at all'*, *'somewhat'*, *'largely'* or *'completely'* (Carson *et al*., 2000*b*). Operational criteria were provided to guide ratings (online Supplementary Table 1). Patients whose symptoms were rated as 'not at all' or only 'somewhat' explained were combined as having 'symptoms unexplained by organic disease'. Neurologists also listed their clinical diagnoses for the patient (up to three allowed, free text) immediately following the initial consultation, prior to any investigations.

Outcome information

Approximately 18 months after the initial consultation we sought information about the patients' diagnosis from four sources. First, a questionnaire was sent to the patients' primary care doctors reminding them of the neurologist's initial diagnoses and 'organicity' rating. It asked them to report: (i) any new medical events; (ii) what these had been; and (iii) whether, in the general practitioner's (GP) opinion, these new findings provided a better explanation for the patient's original symptoms. Second, all deaths were identified via NHS Scotland's Information and Services Division's database and death certificates. Third, in all patients in whom the above had suggested a possible change in diagnosis the original neurologist was asked whether: (i) an organic diagnosis had been considered at the first consultation; (ii) investigations had been ordered that led to the later

diagnostic revision; and (iii) follow-up had been arranged to monitor the patient. We also reviewed the original clinic letters and sought clarification from GPs when necessary.

Baseline and outcome data on other variables were collected and are reported elsewhere (Sharpe *et al*., 2009).

Analysis

Proportion with symptoms 'unexplained' by organic disease

The proportions of patients with symptoms 'completely', 'largely', 'somewhat' and 'not at all' explained by 'organic disease' were determined. The mean age in each category and proportion of females in each category were calculated. We also compared these proportions across the four regional centres.

Neurologist's initial diagnoses

The diagnoses recorded by the assessing neurologist were placed by consensus into categories designed by the investigators (J.S., R.D. and R.R.) and based on those used in previous studies [Hopkins *et al*., 1989; Perkin 1989; Stevens 1989; Association of British Neurologists (Service Committee) 1991; Wiles and Lindsay 1996; Maddison 2005]. Where a differential diagnosis was given, the first diagnosis was used for the purpose of categorization. In cases where the diagnosis was unclear, the neurologist's 'unexplained' rating was also used to clarify the categorization. For example, a diagnosis of 'Back pain—cause uncertain' when accompanied by a rating of 'somewhat' or 'not at all' explained was classified as 'Pain symptom—somewhat or not at all explained'. Where a neurologist had only offered a 'possible' diagnosis this was categorized as if the diagnosis was more certain. For example a diagnosis of 'possible multiple sclerosis' was categorised as 'multiple sclerosis'.

Diagnosis at follow-up

A change in the initial diagnosis at follow-up may indicate that the original diagnosis was wrong. However, it may also indicate a difference of clinical opinion between the doctor who made the initial assessment and those who saw the patient subsequently, the removal of one diagnosis when several initial diagnoses were made, or a refinement of the initial diagnosis. Previous studies of 'misdiagnosis' have not clearly differentiated between these various types of diagnostic change, despite their very different significance for doctor and patient. We therefore devised a new classification of diagnostic change to better reflect this complexity (J.S.) (Table 1). Allocation of cases to this classification was made by consensus (A.C., J.S., C.W. and M.S.) using all the available information. Results are presented for all patients in whom either the primary care doctor or consensus panel thought there may have been a diagnostic change (shown as Stage 2 in Fig. 2).

Results

Recruitment

Between 16 December 2002 and 26 February 2004, 4299 patients attended as new patients to the specified clinics. Figure 1 shows the process of recruitment and reasons for exclusions. The final

Table 1 A new classification of diagnostic revision used in the study

Type of diagnostic revision		Example	Degree of clinician error
1	Diagnostic error	Patient presented with symptoms that were plausibly due to multiple sclerosis. The diagnosis of multiple sclerosis had not been considered and was unexpected at follow-up.	Major
2	Differential diagnostic change	Patient presented with symptoms that were plausibly related to a number of conditions. Doctor suggested chronic fatigue syndrome as most likely but considered multiple sclerosis as a possible diagnosis. Appropriate investigations and follow-up confirmed multiple sclerosis.	None to minor
3	Diagnostic refinement	Doctor diagnosed epilepsy but at follow-up the diagnosis is refined to juvenile myoclonic epilepsy.	Minor
4	Comorbid diagnostic change	Doctor correctly identified the presence of both epilepsy and non-epileptic seizures in the same patient. At follow-up, one of the disorders has remitted.	None
5	Prodromal diagnostic change	Patient presented with an anxiety state. At follow-up the patient has developed a dementia. With hindsight, anxiety was a prodromal symptom of dementia but the diagnosis could not have been made at the initial consultation as the dementia symptoms (or findings on examination or investigation) had not developed.	None
6	*De novo* development of organic disease	Patient is correctly diagnosed with chronic fatigue syndrome. During the period of follow-up, the patient develops subarachnoid haemorrhage as a completely new condition.	None
7	Disagreement between doctors—without new information at follow-up	Patient is diagnosed at baseline with chronic fatigue syndrome and at follow-up with chronic Lyme disease by a different doctor even though there is no new information. However, if the two doctors had both met the patient at follow-up, they would still have arrived at the same diagnoses. This would be reflected in similar divided opinion among their peers.	None
8	Disagreement between doctors—with new information at follow-up	Patient is diagnosed at baseline with chronic fatigue syndrome and at follow-up with fatigue due to a Chiari malformation by a different doctor because of new information at follow-up, (in this case an MRI scan ordered at the time of the first appointment). However, the first doctor seeing the patient again at follow-up continues to diagnose chronic fatigue syndrome believing the Chiari malformation to be an incidental finding. This would be reflected in divided opinion among their peers.	None

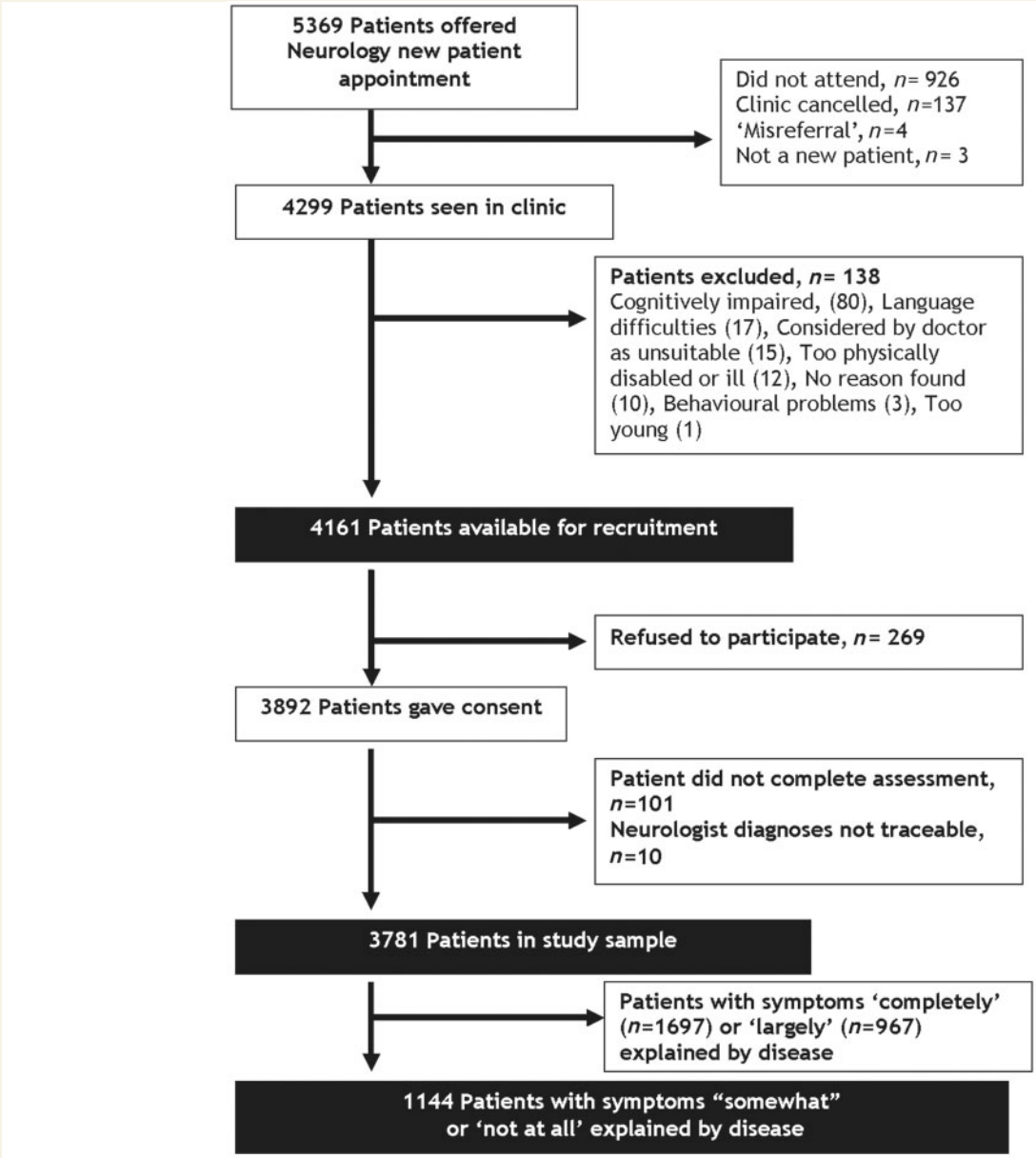

Figure 1 Flow chart of patient recruitment into study.

sample included 3781 patients (88% of all attendees and 91% of all eligible new out-patients).

Proportion with symptoms unexplained by organic disease

In total, 1144 patients (30% of the total) were rated by the assessing neurologists as having symptoms 'not at all' [$n = 446$ (12%)] or 'somewhat explained' [$n = 698$ (18%)] by organic disease. Table 2 shows the association of age and gender with the extent to which the symptoms were explained. Unexplained symptoms were associated with younger age and female gender (both $P < 0.001$ by one-way analysis of variance (ANOVA) and chi-squared test, respectively). There were only minor differences in the proportion of patients in the 'somewhat explained' and 'not at all explained' categories across the four regional centres in Scotland: Aberdeen 32%, Dundee 26%, Edinburgh 30% and Glasgow 30%.

Neurologist's initial diagnoses

Table 3 shows the initial diagnoses given by the neurologist to the 1144 patients with symptoms 'not at all' or 'somewhat' explained by organic disease. Among them, 293 (26%) had a neurological disease diagnosis (but with symptoms rated as unexplained by that disease) and 292 (26%) had a headache diagnosis. It is notable that 209 patients had a diagnosis of a conversion symptom (18%). The remaining 350 patients (31%) had another 'functional' or psychological diagnosis (Table 3).

Diagnosis at follow-up

GPs responded to the request for follow-up information in 1095 (96%) cases. In 65 cases they were unable to provide information (most commonly because the patient had left the practice). Consequently, usable follow-up data were available for 1030 (90%) of patients (Fig. 2). The median interval between the initial neurology appointment and receiving the GP's follow-up data was 577 days (1 year 7 months; inter-quartile range 535–601 days).

The process of diagnostic review is described in Fig. 2. The main finding was that in only four of 1030 cases on which we had follow-up information (0.4%; 95% CI 0.1%–1.0%) did an unexpected 'organic' disease diagnosis emerge during follow-up (Table 4). We have classified this as a 'Category 1' diagnostic revision (Table 1). In two of these cases, whilst the neurologist had made a judgement that the symptoms were not due to organic disease, they had ordered investigations that led to the subsequent (follow-up) diagnosis being made.

There were a number of patients in whom a 'Category 1' diagnostic revision appeared to have occurred but for whom careful review of the data revealed that this was not the case. Table 5 shows the other types of diagnostic revision. Most common were patients in whom a differential diagnosis had been considered at the initial assessment and was confirmed at follow-up ($n = 12$) (Category 2). In one case there appears to have been a *de novo* development of organic disease (Category 6). There were six cases in which there was disagreement between doctors about what the correct follow-up diagnosis was (Categories 7 and 8).

Eight patients had died by the time of follow-up. For three of these there was no plausible connection between their initial

Table 2 The degree to which neurologists rated symptoms as explained by organic disease in 3781 new out-patients

Symptom rating	*n* (%)	Age (mean, years)	Female (%)
Not at all explained by disease	446 (12)	41	68
Somewhat explained by disease	698 (18)	45	63
Largely explained by disease	940 (25)	47	58
Completely explained by disease	1697 (45)	48	51
Total	3781 (100)	46	57

Unexplained symptoms were associated with younger age and female gender (both $P < 0.001$ by one-way ANOVA and chi-squared test, respectively).

Table 3 Diagnoses in 1144 new neurology out-patients in whom presenting symptoms were rated as 'not at all' ($n = 446$) or 'somewhat explained by organic disease' ($n = 698$)

Neurologist diagnosis	Number of patients, *n* (% of 1144 patients)	Age (mean, years)	Female *n* (%)
Neurological disease but symptoms rated as 'unexplained' by that disease[a]	293 (26)	47	171 (58)
Headache	292 (26)		
Other headache	153	43	96 (63)
Tension headache	90	41	49 (54)
Migraine[b]	49	44	41 (84)
Conversion symptoms	209 (18)		
Non-epileptic attacks/dissociative seizures	85	38	62 (73)
Functional sensory[c]	68	44	36 (53)
Functional weakness/gait/movement[d]	56	45	45 (80)
Other			
Functional[e]	107 (9.0)	43	72 (67)
Primary psychiatric diagnosis[f]	77 (6.7)	43	58 (75)
Pain symptoms[g]	63 (5.5)	46	48 (76)
Dizzy symptoms—NE or SE	32 (2.8)	45	24 (75)
Fatigue symptoms—NE or SE	29 (2.5)	43	25 (86)
Cognitive symptoms—NE or SE	22 (1.9)	44	9 (41)
Post-traumatic[h]	20 (1.7)	34	11 (55)
Total	1144		747 (65)

NE or SE = not explained or somewhat explained by organic disease.
a Epilepsy (31), peripheral nerve disorders (48), 'other' neurological (49), multiple sclerosis/demyelination (32), spinal disorders (36), movement disorders (20), syncope (25), stroke/transient ischaemic attack (17), general medical (25), brain tumour (6), muscle/neuromuscular (3), dementia (1) and motor neurone disease(0).
b Migraine was classified as a neurological disease in the guidance given to neurologists completing this study. However, there were 49 patients with migraine whom the neurologist rated as having symptoms 'not at all' or 'SE' by disease.
c Hemisensory (12), other functional sensory (54), visual (2).
d Weakness (35), mixed motor/sensory (10), movement disorder (9), gait (2).
e 'Non-organic' (50), no diagnosis—NE or SE (22), possibly non-organic (15), physiological (9), hyperventilation (8), functional and organic (3).
f Alcohol excess (3), anxiety and depression (68), other psychiatric (5), psychosis (1).
g Pain symptoms NE or SE (35), spinal pain NE or SE (12), atypical facial/temporomandibular joint pain (9) and fibromyalgia (7).
h Post-head injury symptoms—NE or SE (19), repetitive strain injury (1).

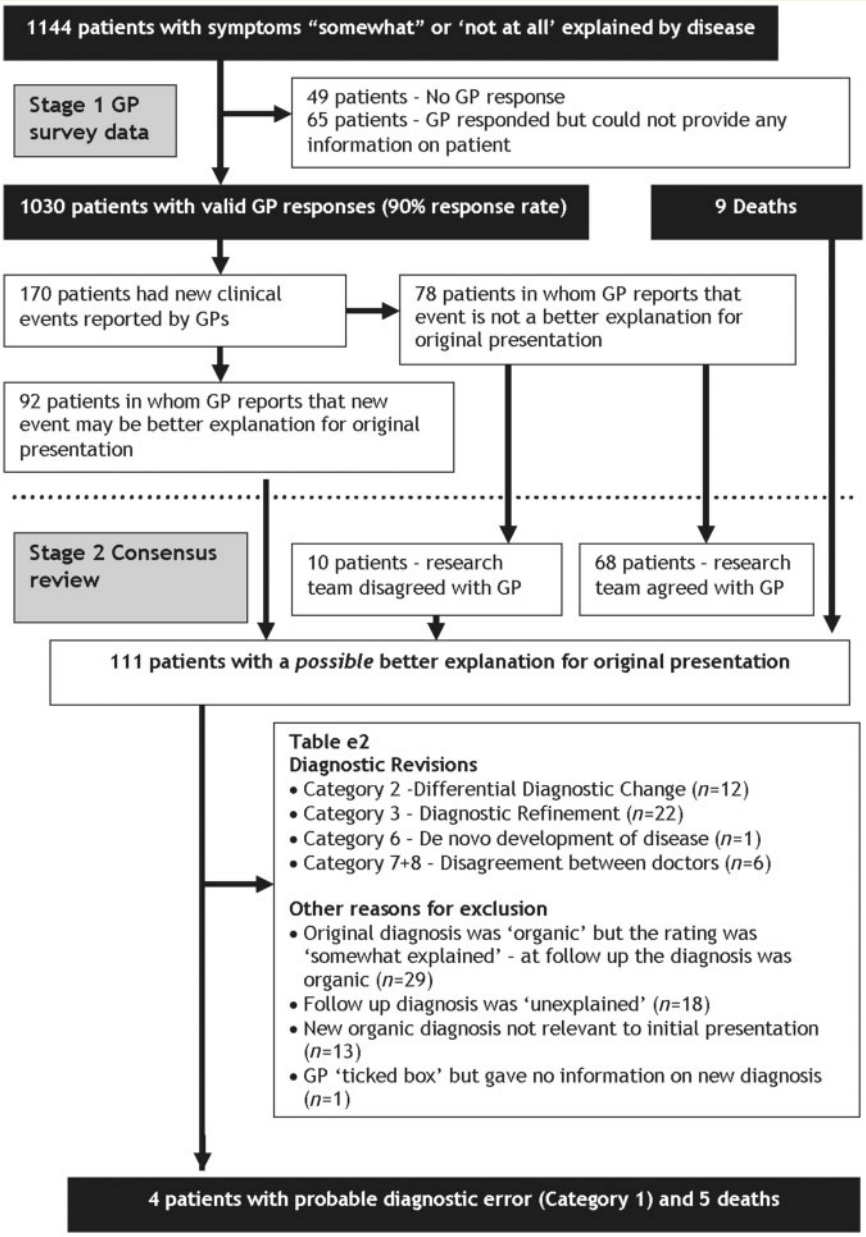

Figure 2 Response rate and subsequent diagnostic revision for the 1144 patients diagnosed with 'symptoms unexplained by organic disease' at initial consultation.

neurological diagnosis and their death (Supplementary Table 2). However, it was striking that for five of the remaining patients the initial diagnosis had been that of non-epileptic attack disorder, representing a case fatality of 5% (4 out of 80) for this diagnosis (Table 6). For Case 25, the initial diagnosis of non-epileptic attacks may have been wrong as the patient was subsequently admitted with uncontrolled seizures and died of sepsis. In two cases (Cases 26 and 27) the deaths were due to falls of uncertain origin. In the two final deaths in this group, subarachnoid haemorrhage and myocardial infarction were unlikely to relate to the initial diagnosis.

Detailed information was obtained on a further 83 patients for whom the GP ($n = 73$) or researchers ($n = 10$) thought there may be possibly a new organic diagnosis at follow-up that better explained the original presentation. These did not meet criteria for any of the diagnostic revisions categorized in Table 1 (Supplementary Table 2).

Because of the small numbers of patients with each type of diagnostic revision it was not possible to identify what initial factors or diagnostic subcategory predicted a change in diagnosis at follow-up.

Discussion

This study of 36 neurologists and 3781 patients found that around one-third of all new neurology out-patients present with

Table 4 Patients with Category 1 diagnostic revision—diagnostic error

Case no.	Age/sex[a]	Baseline diagnosis	Neurologist baseline rating	Follow-up diagnosis	Decision making at first consultation			Notes
					Organic diagnosis considered?	Investigations ordered?	Follow-up arranged?	
1	52F	Panic attack, intermittent right-sided weakness	NE	Multiple sclerosis	No	Yes	No	Neurologist did order CT for reassurance which was normal. Subsequent re-referral led to diagnosis.
2	71F	Anxiety	NE	Alzheimer's disease	Yes	Yes	Yes	Neurologist's opinion is that anxiety was prodromal to the development of Alzheimer's disease but memory symptoms were present at start.
3	34F	Atypical facial pain	NE	Brain stem pilocytic astrocytoma	Yes	Yes	Yes	Neurologist ordered investigations but appeared to consider diagnosis to be 'non-organic'. Subsequently congratulated by surgeon on picking up the lesion!
4	46F	Migraine; ?C2 Neuralgia	SE	Chiari malformation type 1	Yes	No	Yes	Had considered other neurological diagnoses but did not pick up Chiari malformation that was plausibly related to headache (but may not be).

a At time of recruitment.
NE = not at all explained by organic disease; SE = somewhat explained by organic disease.

symptoms that are regarded by the assessing neurologist as only 'somewhat' or 'not at all 'explained by organic disease. Patients presenting with unexplained symptoms tended to be younger and were more likely to be female. This finding is consistent with that of previous studies which have reported that 26%–45% of neurology out-patients have a presenting symptom that is rated by the assessing neurologist as unexplained by organic disease (Table 7). Other studies looking at all symptoms (and not just the presenting one) that have reported a frequency of up to 62% (Nimnuan *et al*., 2001; Fink *et al*., 2005). Headache disorders, neurological disorders with 'unexplained' symptoms and conversion symptoms were the commonest diagnostic categories recorded in this study.

We found that after 19 months follow-up, only four (0.4%) of the patients still alive had acquired a new organic disease diagnosis that was both unexpected at the initial neurological assessment and provided better explanation for the patient's original symptoms. When we examined the nature of the diagnostic revisions we found that in many, the original clinical correspondence indicated that the 'revised' diagnosis had been explicitly considered at the initial consultation, or that the investigations that led to the change in diagnosis had been set in train at that time. Patients with neurological symptoms unexplained by organic disease were usually correctly identified as such at their initial clinical assessment. Importantly, this was usually before any investigations had taken place.

It was striking that five of the eight deaths that occurred during follow-up were in patients with an initial diagnosis of non-epileptic attacks. It was not possible to establish whether these deaths were due to undiagnosed epilepsy, unrelated pathology or psychopathology that might be associated with non-epileptic attacks. Previous studies have reported that patients with non-epileptic attacks are at risk of iatrogenic harm, especially in intensive care units (Reuber *et al*., 2000). Other studies have reported that suicide and suicidal ideation are common in this patient group (Crimlisk *et al*., 1998; Carson *et al*., 2000a).

The acquisition of a new organic disease diagnosis that was not considered at the initial assessment and, with hindsight, explained the initial symptoms (Category 1 diagnostic revision), is the one that most doctors think of in terms of 'getting the diagnosis wrong'. However, we found that there are other reasons for diagnostic revision and that previous studies have tended to inflate the perceived risk of 'getting the diagnosis wrong' by amalgamating these (Table 1). For example, in the influential study reported by Slater in the 1960s (Slater, 1965; Slater and Glithero, 1965) there were at least 19 patients with a co-morbid diagnostic revision (Category 4) and others in which the change in diagnosis was related to a change in terminology (e.g. atypical migraine changing to basilar migraine) (Category 7) or in interpretation of tests (e.g. a patient initially diagnosed with hysteria said to be misdiagnosed because of a follow-up diagnosis of 'cortical atrophy') (Category 8).

Our study also highlights the importance of separating out differential diagnostic change (Category 2) as a distinct category. For example, for Case 5 the neurologist had considered the diagnosis as 'probable non-epileptic attacks but possibly frontal lobe epilepsy'. Videotelemetry provided evidence that the diagnosis was epilepsy.

Over a period of follow-up, a patient with 'non-organic' symptoms is at risk of developing a neurological disease simply by chance [see Case 6 (Table 3) and Case 77 (Supplementary Table 2)]. The fact that doctors sometimes simply disagree with each other about the appropriate diagnosis has also been overlooked in previous studies. In this study, six cases fell in to this category (Cases 18–23). For example, in Case 21, despite the same information, one neurologist thought the diagnosis was

Table 5 Other categories of diagnostic revision in which no major error was found

Type of diagnostic revision[a]	Case no.	Age/sex (M/F)	Baseline diagnosis	Neurologist rating[b]	Outcome diagnosis	Decision making at first consultation		
						Outcome diagnosis considered at baseline?	Investigations ordered?	Follow-up arranged?
2	5	19M	Non epileptic attacks	NE	Frontal lobe epilepsy	Yes	Yes	Yes
2	6	35F	Cramp ?cause	SE	Young onset amyotrophic lateral sclerosis	Yes	No	Yes
2	7	69M	Poor balance ?cause Intermittent vertigo	SE	Small cerebellar infarct			
2	8	59M	Somatoform disorder/ depression	NE	Sensory peripheral neuropathy	Yes	Yes	Yes
2	9	45M	Muscle spasm affecting abdomen ?psychogenic ?segmental myoclonus	SE	Spinal segmental myoclonus	Yes	Yes	Yes
2	10	57F	Shaking attack ?cause	NE	Cerebral meningioma	Yes	Yes	Yes
2	11	33M	Paraesthesia ?cause	SE	Multiple sclerosis	Yes	Yes	Yes
2	12	40M	?Demyelination ?Functional	SE	Multiple sclerosis	Yes	Yes	Yes
2	13	29F	?Chronic fatigue	SE	Multiple sclerosis	Yes	Yes	Yes
2	14	68F	Blackouts ?seizure ?psychogenic	SE	Epilepsy	Yes	Yes	Yes
2	15	66M	Headache (recent onset)	SE	Chronic Subdural Haematoma	Yes	Yes	Yes
2	16	39F	Left sided weakness	NE	Migraine	Yes	Yes	Yes
6	17	46F	Depression; Headaches; Post traumatic encephalopathy	NE	Optic neuritis	No	No	No
7	18	62F	?anxiety attacks, past history epilepsy, colloid cyst third ventricle	SE	Epilepsy	Yes	Yes	Yes
7	19	66F	Non-specific longstanding aches	NE	Osteoarthritis/trochanteric bursitis	Yes	No	No
7	20	50M	Back pain	NE	Plates in back to be removed	Yes	No	No
7	21	53F	Probable somatisation disorder	NE	Possible multiple sclerosis	Yes	Yes	No
8	22	76F	Tension headache	NE	Cervical spondylosis	Yes	No	No
8	23	58F	Left sided sensory loss—aetiology unclear	SE	Demyelination (according to GP). Non-specific changes on MRI (according to neurologist)	Yes	Yes	Yes

M = Male, F = Female
a See Table 1.
b Baseline neurologist rating of symptoms.
NE = not at all explained by organic disease; SE = somewhat explained by organic disease

somatization disorder rather than multiple sclerosis and a second neurologist took the opposite view. In the light of the many different types of diagnostic revision that can occur we suggest that future studies consider and report diagnostic revisions in a similar operationalized manner.

There have been few previous similar studies. Our own previous study systematically reviewed studies of diagnostic revision at follow-up in patients with an initial diagnosis of conversion symptoms or 'hysteria' (Stone *et al*., 2005). Conversion symptoms refer to motor or sensory symptoms or blackouts unexplained by neurological disease and represent a subset of the patients followed up in this study. We found that the early studies were of very poor quality but that, since the early 1970s the proportion in which a serious diagnostic revision had been recorded was low (4%) (Stone *et al*., 2005). However, our conclusions had to be tentative as the available studies were nearly all retrospective, single centre studies of small numbers of patients, usually of in-patients rather than out-patients and often low in methodological quality. There have also been previous studies of the outcome of specific symptoms in primary care including chronic fatigue (Kroenke *et al*., 1988), dizziness (Kroenke *et al*., 1992), diarrhoea (Hawkins and Cockel, 1971) and palpitations (Sox Jr *et al*., 1981) suggesting that serious organic disease rarely emerges. Whilst one study reported an association between unexplained widespread pain and increased mortality (Macfarlane *et al*., 2001), a recent and similar study did not (Macfarlane *et al*., 2007).

Limitations

The method of follow-up that we used—seeking information primarily from the patient's GP—has limitations. A formal re-evaluation using a standardized re-examination by an independent neurologist including appropriate investigations would have

Table 6 Recorded cause of death at follow-up in five patients, rated at baseline as having symptoms either 'not at all' or only 'somewhat' explained by organic disease in whom the death could conceivably have related to the initial presentation

Case no.	Age/ sex[a]	Baseline diagnosis	Rating[b]	Cause of death	Additional information	Category of diagnostic revision[c]
25	41F	Non-epileptic seizures	NE	1. Bronchopneumonia 2. Leber's hereditary optic atrophy 3. Renal failure	Patient admitted to hospital with uncontrolled seizures and sepsis. Bronchopneumonia occurred 3 months after admission	Possible Category 1
26	59F	Non-epileptic attack disorder	NE	1. Positional asphyxia secondary to fall and entrapment indoors 2. Toxicology—not significant	Longstanding depression	Uncertain if revision required
27	46F	Previous aneurysm Probable non-epileptic attack	SE	1. External haemorrhage 2. Laceration to neck 3. Fall down stairs	Alcohol and forensic history just prior to death	Uncertain if revision required
28	36M	Epilepsy or syncope or non-epileptic attack disorder	SE	1. Right large cerebral infarction secondary to vasospasm after aneurysm clipping for subarachnoid haemorrhage 2. Meningitis 3. Electrolyte disturbance	No data	6
29	58F	Non-epileptic attack	NE	1. Myocardial infarction	Neurologist adamant that attacks were non-epileptic and myocardial infarction not relevant	6

a At time of diagnosis.
b Baseline Neurologist Rating of Symptoms.
c See Table 1.
NE = not at all explained by organic disease; SE = somewhat explained by organic disease

Table 7 Comparison of previous studies of the frequency of symptoms unexplained by organic disease in neurology out-patients

Study, year of publication	Location	*n*	Per cent unexplained by organic disease
Carson *et al*., 2000*b*	Edinburgh, UK	300	30% (11% 'not at all' and 19% 'somewhat' explained by organic disease)
Bateman and Harrison, 2000	Bath, UK	356	26% no neurological disorder
Nimnuan *et al*., 2001	London, UK	103	62% had 'medically unexplained' symptoms
Stone *et al*., 2002	Edinburgh, UK	89	36% (7% 'not at all' and 29% 'somewhat' explained by disease)
Stone *et al*., 2004	Colchester, UK	100	45% had a 'non-neurological' diagnosis
Snijders *et al*., 2004	Utrecht, Netherlands	208	35% considered to have 'medically unexplained' symptoms
Fink *et al*., 2005	Vejle, Denmark	198[a]	61% had 'medically unexplained' symptom, 39% had a somatoform disorder
This study, 2009	Aberdeen, Dundee, Edinburgh, Glasgow, UK	3781	30% (12% 'not at all' and 18% 'somewhat' explained by organic disease)

a Mixture of in- and out-patients.

been more robust but was not feasible with this size of study. Future studies could examine all or a subsample of followed-up patients according to this gold standard. Consequently, it is possible that primary care doctors did not identify manifestations of neurological disease (such as mild multiple sclerosis) and also that they were biased against doing so because of the neurologist's initial diagnosis.

The duration of follow-up was only 19 months and it is possible that new diagnoses, especially of slowly developing disorders such as neurodegenerative disorders, might emerge over a longer period of follow-up.

The study reported here was of NHS neurology practice in Scotland, UK and consequently the findings may not generalize elsewhere. Although all the patients were new referrals from primary care, many had pre-existing neurological conditions. In addition, by sampling from general neurology clinics and excluding specialty clinics, certain conditions (such as stroke/transient ischaemic attack seen in neurovascular clinics) were under-represented. However, all four Scottish neurology centres and almost all Scottish neurologists (as well as their trainees) entered their patients into this study. Ninety-one percent of all patients eligible participated at their initial assessment and information on 90% of those was obtained at follow-up. The case mix of patients was similar to other out-patient neurology case series from the UK [Perkin, 1989; Association of British Neurologists (Service Committee), 1991; J. Stone *et al*., submitted for publication] suggesting that the sample was representative of out-patient neurological practice in the UK.

Some neurologists may have rated a patient's symptoms as 'somewhat explained' mainly because they were depressed or anxious. Others may have used this rating only when the 'physical symptoms' were somewhat explained. It is likely that both kinds of patient exist within our 'somewhat explained' category. We did not examine the inter-rater reliability of the scale which sought to codify an individual clinician's judgement. However, the relative consistency between centres offers some confirmation of consistency of ratings.

We do not have data on how many patients had already had investigations prior to being seen and how this may have influenced the accuracy of the diagnosis. Typically most patients in the study were referred from primary care and would not have had any brain imaging.

Neurologists in most countries do not generally have any postgraduate psychiatric training (Metcalfe *et al*., 1988; Jefferies *et al*., 2006). It is possible, had they been more skilled at detecting psychiatric disorder, that more primary psychiatric diagnoses, such as panic disorder, would have been made.

There was inevitably some judgement involved in our classification of diagnostic revision although we aimed to minimize this by using a consensus review of ratings. We have listed all cases (Supplementary Table 2) for which the GP had reported an organic disease diagnosis that they felt might have explained the original symptoms.

Finally, we acknowledge that the separation of symptoms due to organic disease and not due to organic disease is theoretically problematic. All symptoms, including functional or psychological ones, must have associated neural correlates and mechanisms. Nonetheless, this is the framework that most doctors operate in.

Implications

A third of new out-patients at neurology clinics have symptoms that the assessing neurologist regards as unexplained by organic disease. New diagnoses that explained the original symptoms rarely emerged over the following 18 months in this study. Whilst the diagnoses of 'symptoms unexplained by organic disease' must continue to be made with care, the data presented here suggest that serious diagnostic change after an initial clinical assessment by a consultant neurologist is unusual.

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Supplementary material

Supplementary material is available at *Brain* online.

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