## PAPER

# The outcome of neurology outpatients with medically unexplained symptoms: a prospective cohort study

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**Background:** In a previous cross sectional study of 300 consecutive new attenders at neurology outpatient clinics, 90 were detected with symptoms that were rated as "not at all" or only "somewhat" explained by organic disease.
**Objective:** To report a follow up study of this cohort.
**Methods:** Patients were reinterviewed by telephone eight months after their initial assessment. They were asked to rate their overall improvement on a clinical global improvement scale, and their health status on the medical outcome short form 36 item scale (SF-36). The PRIME MD interview was administered to determine psychiatric diagnoses. Neurological and primary care records were reviewed for any changes in diagnostic opinion during the follow up period.
**Results:** Of the 90 eligible patients, 66 (73%) participated in follow up. Among these, five (8%) rated themselves as "much worse," four (6%) as "somewhat worse," 27 (40%) as "just the same," 15 (23%) as "somewhat better," and 15 (23%) as "much better." There were no cases in which an organic cause for the presenting complaint was uncovered during the follow up period. Poorer physical function at baseline was the only predictor of poorer outcome at follow up.
**Conclusions:** Over half the patients who presented to neurologists with symptoms that were rated as largely or completely medically unexplained had not improved eight months later. In no case was a disease explanation for the original presenting symptoms subsequently identified.

I n an earlier paper "Do medically unexplained symptoms matter?" we found that 30% of new referrals to general neurology outpatient clinics had symptoms which were rated by the assessing neurologist as "not at all" or "somewhat" explained by organic disease.[1] These patients rated their disability as highly as those with identified neurological disease. In addition, they reported higher rates of depression and anxiety disorders. We concluded that medically unexplained symptoms were an important cause of morbidity and that they did indeed matter. However, we were unable to report on prognosis.

Although there are a few outcome studies for specific conversion symptoms such as motor conversion disorder[2–4] and pseudoseizures,[5–7] these represent only a small proportion of patients attending neurological clinics with medically unexplained symptoms (MUS). In addition there have been outcome studies of "hysteria," but these have largely been in psychiatric populations[8–19] or retrospective.[20 21] We are not aware of any studies that have examined the outcome of a range of medically unexplained symptoms in neurological outpatients prospectively.

We therefore conducted a prospective eight month follow up of all the patients who at the initial assessment had symptoms that were rated by the neurologist as "not at all" or only "somewhat" explained by organic disease. Our aims were to determine the degree of global clinical improvement, if any, and the changes in health status and psychiatric status.

## METHODS

### Initial assessment

The initial study has been described in detail elsewhere.[1] In brief, we interviewed a consecutive sample of 300 newly referred general neurology outpatients, 90 of whom were judged by their consultant neurologist to have symptoms that were "not at all" or only "somewhat" explained by organic disease[2 22]; we shall refer to them as having medically

unexplained symptoms (MUS). The assessment recorded health status and mental state using the following measures.

The self rated *medical outcome study scale* (SF-36)[23] was used to measure patients' health status. This widely used self report scale measures health status in eight domains: general health perceptions, physical functioning, physical role functioning, bodily pain, social functioning, vitality, mental health, and emotional role functioning.

The *primary care evaluation of mental disorders* (PRIME MD) is a brief structured interview[24] that was used to make psychiatric diagnoses according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM IV) criteria.[25]

### Follow up assessment

This study is a follow up assessment of the 90 patients with MUS eight months after their initial assessment. The assessment consisted of a self rated five point clinical global improvement (CGI) scale[26] and a repeat of the measures used in the initial assessment. All assessments were made by telephone interview. When a patient had no telephone, or preferred to see the interviewer, or where there was communication difficulty, a face to face interview was conducted. Good agreement has been reported between telephone and face to face diagnostic interviews.[27] The interviews were conducted by AC and KP, both of whom had been trained in psychiatric diagnostic assessment.

The patients' neurology and general practice case notes were also examined at follow up, and the cases discussed with the relevant clinician where necessary, in order to record any change in diagnostic opinion.

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**Abbreviations:** CGI, clinical global improvement scale; DSM IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; MUS, medically unexplained symptoms; PRIME MD, primary care evaluation of mental disorders; SF-36, short form 35 item medical outcome study scale

**Table 1** Comparison of patients followed up with those not followed up according to baseline characteristics

|  | Followed up | Not followed up | p Value |
|---|---|---|---|
| Number | 66 | 24 | |
| Mean age | 42 | 39 | 0.36* |
| Number male | 24 (36%) | 9 (38%) | 0.9† |
| Number with emotional disorder | 44 (67%) | 16 (67%) | 1† |

*Student's t test.
†χ² test.

**Table 2** The eight month self rated clinical global improvement (n=66)

| Clinical global improvement | Number of subjects | Per cent (95% CI) |
|---|---|---|
| Much worse | 5 | 8% (3% to 17%) |
| Somewhat worse | 4 | 6% (2% to 15%) |
| Just the same | 27 | 41% (29% to 54%) |
| Somewhat better | 15 | 23% (13% to 35%) |
| Much better | 15 | 23% (13% to 35%) |

CI, confidence interval.

The study was approved by the local research ethics committee.

### Analysis

First, we made a comparison of the findings at initial assessment between those who participated in follow up and those who did not, in order to assess the possibility of systematic bias in the follow up sample. Second, we described the clinical global improvement and changes in health status and mental state of the patients followed up. Third, we examined the findings at baseline by clinical global improvement in order to identify possible predictors of poor outcome. We would have liked to conduct regression analyses but felt that small numbers prohibited such a strategy.

## RESULTS

Of the 90 patients who initially presented to general neurology clinics with symptoms that were medically unexplained, 66 (73%) participated in the follow up assessment. The mean age of those who participated was 42 years; 24 (36%) were male and 42 (64%) female. There were no substantive or statistically significant differences between those subjects who did and did not participate (table 1).

The clinical global improvement scores are shown in table 2. It can be seen that 36 of the sample (55%; 95% confidence interval (CI), 42% to 67%) remained the same or got worse, compared with 30 (45%; 95% CI, 33% to 58%) who improved. Clinical global improvement was associated with improvement across a range of functions including physical function, degree of pain, social function, and mental state. Those who rated themselves as improved reported significantly greater improvement across all SF-36 scores and had fewer anxiety or depressive disorders at follow up (table 3).

Review of the neurological case records was completed for all 90 patients. Review of the primary care records was only possible for 58 of the 66 patients who participated in follow up (in three cases the patients did not wish their general practice case records to be reviewed and in the other five cases the general practitioners refused permission despite the patients

**Table 3** The eight month outcome in terms of health status and mental state, also showing results by dichotomy of global clinical improvement into "same or worse" or "improved" (n=66)

|  | Whole cohort | Same or worse | Improved |
|---|---|---|---|
| Number (per cent, 95% CI) | 66 | 36 (55%, 42% to 67%) | 30 (45%, 33% to 58%) |
| Mean change in SF-36 score* | | | |
| Change in physical function | −2 (−6 to 2) | −9 (−14 to −8) | 7 (2 to 12) |
| Change in physical role functioning | 11 (0 to 22) | −8 (−21 to 6) | 34 (20 to 48) |
| Change in bodily pain | 7 (1 to 13) | −1 (−7 to 6) | 17 (7 to 27) |
| Change in social function | 5 (−3 to 13) | −6 (−17 to 5) | 19 (10 to 29) |
| Number with emotional disorder† at follow up (per cent, 95% CI) | 42 (63%, 51% to 75%) | 30 (83%, 67% to 93%) | 12 (40%, 22% to 59%) |

*Although the raw SF-36 scores had a non-parametric distribution, the "change" scores followed a normal distribution.
†Emotional disorder is any of the following DSM IV diagnoses: major depressive disorder, minor depressive disorder, dysthymia, panic disorder, generalised anxiety disorder, anxiety disorder NOS as identified on the PRIME MD interview.
CI, confidence interval; DSM IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; PRIME MD, primary care evaluation of mental disorders; SF-36, short form 35 item medical outcome study scale.

**Table 4** Predictors from baseline assessment of eight month outcome (n=66)

|  | Same or worse | Improved | p Value |
|---|---|---|---|
| Number (per cent, 95% CI) | 36 (55%, 42% to 67%) | 30 (45%, 33% to 58%) | |
| Mean age (years) (95% CI) | 43 (39 to 47) | 39 (35 to 43) | 0.4* |
| Number male (per cent, 95% CI) | 11 (31%, 16% to 48%) | 13 (43%, 26% to 63%) | 0.3† |
| Median SF-36 score (95% CI) | | | |
| Physical function | 68 (45 to 90) | 85 (70 to 95) | **<0.02‡** |
| Physical role functioning | 37 (0 to 75) | 37 (0 to 100) | 0.6‡ |
| Bodily pain | 41 (32 to 62) | 62 (41 to 74) | 0.1‡ |
| Social function | 62 (50 to 62) | 75 (50 to 100) | 0.1‡ |
| Number with emotional disorder§ at baseline assessment (per cent, 95% CI) | 26 (72%, 61 to 83%) | 18 (60%, 48 to 72%) | 0.3† |

*Student's t test.
†χ² test.
‡Kruskall Wallis test for comparison of medians and non-parametric confidence intervals.
§Emotional disorder is any of the following DSM IV diagnoses: major depressive disorder, minor depressive disorder, dysthymia, panic disorder, generalised anxiety disorder, anxiety disorder NOS as identified on the PRIME MD interview.
CI, confidence interval; DSM IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; PRIME MD, primary care evaluation of mental disorders; SF-36, short form 35 item medical outcome study scale. 1

having given permission). Review of all the available notes revealed no cases where further assessment or investigation (by neurologist, general practitioner, or other medical specialist) had uncovered an organic disease as an explanation for the presenting complaint.

There was no substantial difference in mean age or sex between those who improved and those who did not (table 4). The only baseline variable with a statistically significant association with poor outcome was a lower score on the physical function subscale of the SF-36. There were also non-significant associations with lower scores on the other subscales of the SF-36.

## DISCUSSION

Over half the patients who presented to neurologists with medically unexplained symptoms had not improved when they were reviewed eight months after their initial consultation. Patients' physical disability, ability to carry out daily activities, pain symptoms, social function, and mental health changed in line with their self rated overall clinical outcome. No cases of new neurological disease were discovered during the follow up period. Patients with worse physical function at baseline had a worse outcome.

Of previous studies, the one most similar to this is that of Jacobs and Russell, published in 1961.[20] They conducted a retrospective review of 92 consecutive patients with MUS five years after their initial presentation to neurologists in Oxford during the mid 1950s. They found that 33% still had "minor symptoms" but they did not measure health status or outcome. Only five cases had developed a previously undetected disease which explained the presenting complaint.

There are no other studies with which we can directly compare our results. However, other studies which have examined MUS in neurological inpatient populations[8 21] or in patients referred to psychiatry services,[9-19] or which have concentrated on specific subgroups of patients with MUS such as motor conversion disorder[2-4] and pseudoseizures,[5] are of interest. Unfortunately, prospective studies in any population[4 6 7] are rare. Although the sampling methods, populations, and outcome measures used in these studies vary widely, most have nonetheless found that between 40% and 60% of patients remain symptomatic. Furthermore, it is notable that the observed rate of misdiagnosis in studies of hysteria, conversion disorder, and of individual symptoms has fallen from 10–15% (or higher in the case of Slater's study[21]) in the 1960s and 70s[8-10 21] to figures of less than 5% in more recent studies.[2-4] In fact, while the clinicians' usual concern seems to be to avoid misdiagnosing organic disease as functional, we note the warnings of Nimnuan et al,[28] that misdiagnosis in the opposite direction is much more common. For example in one large series of patients diagnosed with multiple sclerosis 9% turned out not to have any organic disease.[29]

The evidence for baseline predictors of poor outcome from these studies is inconclusive and at times contradictory. Probably the only consistent findings are that a short duration of symptoms predicts better outcome,[2 4 19] and possibly personality disorder predicts a worse outcome.[4 7 10]

The results from neurological samples seem to be in keeping with those found elsewhere. The World Health Organisation's study of unexplained symptoms in primary care is the largest available prospectively collected dataset. The study involved assessment of 5438 subjects from 15 centres around the world.[30] The investigators found that 20% of subjects reached the study criteria for a somatoform disorder. They managed to re-examine 67% of them 12 months later and found that 49% were still symptomatic.

Our findings must be considered in the context of methodological limitations, some of which have been described previously.[1] The principal limitation is the loss from follow up of 24 of the 90 patients (27%). Although there is little evidence to suggest systematic bias, the outcome of the patients who were not included in the follow up remains unknown. Nonetheless, even if it is assumed that all these patients had fully recovered, 40% of patients would still have been rated as unchanged or worse, and a further 17% improved but symptomatic. Second, we were only able to review the general practitioners' notes in 58 patients (64%). Third, patients were not subjected to a neurological examination at the time of follow up. Finally, a lack of statistical power means that any statement on baseline predictors of poor outcome should be treated with caution.

Our previous study showed that MUS were associated with clinically significant morbidity at the time of initial presentation. The findings presented here show that approximately half those patients continue to suffer significant morbidity eight months later, despite having had the benefit of a neurological consultation.

Randomised controlled trials of other samples of patients with MUS have shown that treatment can be effective in improving specific outcomes. These treatments include structured management in primary care,[31] tricyclic (and possibly SSRI) antidepressants,[32] and cognitive behavioural therapy.[33] There is now an urgent need for large scale studies of neurological patients to determine what baseline factors predict poorer outcome, and what treatments are effective and feasible in this setting.

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