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ORIGINAL ARTICLE

Depression in adults with Fabry disease: A common and under-diagnosed problem

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Summary
Background Anderson–Fabry disease (AFD), an X-linked lysosomal storage disorder, leads to multi-organ dysfunction and premature mortality. Depression in adults with AFD has been reported, but no large study has been done. We have examined the adult Fabry population in the United Kingdom to describe the prevalence, associated factors and frequency of diagnosis of depression.
Methods Postal questionnaires were sent from four adult clinics to 296 AFD patients. A response rate of 62% (n=184; 74 male, 110 female) formed the data set. Questionnaires collected demographic and Fabry-specific information. Depression status was assessed using the Centre for Epidemiological Studies depression scale (CES-D).
Results Responders were aged between 18 and 76 years (mean 44). The prevalence of depression was 46%, of which 28% were consistent with 'severe clinical depression'. Unlike the normal population, males with AFD report a higher prevalence of severe depression than females (36% males; 22% females). Interference of AFD symptoms with individuals' lives (particularly acroparaesthesiae or anhidrosis) showed the largest odds of association with depression. Relationship and financial status proved strong predictors of depression: 88% of those with mild-moderate depression and 72% with severe depression were undiagnosed.
Conclusion Depression is common and under-diagnosed in AFD. Proper assessment of and treatment for depression could improve the quality of life of these patients.

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References to electronic databases: Anderson–Fabry disease: OMIM 301500. α-Galactosidase A: EC 3.2.1.22)

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Abbreviations

AFD	Anderson–Fabry disease
CES-D	Centre for Epidemiological Studies – Depression
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ERT	enzyme replacement therapy
α-GAL	α-galactosidase
HRQOL	Health-Related Quality of Life
WHO	World Health Organization

Introduction

AFD (OMIM 301500) is a rare X-linked lysosomal storage disorder resulting from deficient activity of α-galactosidase A (α-gal A; EC 3.2.1.22) leading to the

progressive accumulation of glycosphingolipids. With increasing age, these depositions accumulate throughout the body and lead to a multi-system disorder, particularly affecting the kidney, heart and brain, associated with chronic symptoms such as pain and asthenia.

Depression is a global issue of increasing proportions. The complex relationship between chronic physical conditions and depression has been documented in many studies (Aneshensel et al 1984; Ettinger et al 2004; Katon 2003; Patten 1999; Polsky et al 2005; Raphael 2005; Vilhjalmsson 1998). In particular, there is a strong association of chronic pain with depression (Dersh et al 2002). As a chronic disease in which pain is a major feature, AFD would be expected to carry an increased risk of depression.

Despite case reports of AFD patients suffering from depression dating back more than 40 years (Guin et al 1976; Liston et al 1973; Wise et al 1962), systematic research on depression in this group has been limited (Hoffmann 2006). Small retrospective studies of male patients have shown an incidence of depression between 18% (Grewal 1993) and 20% (MacDermot et al 2001). Major depression has also been reported in four female AFD carriers (Sadek et al 2004). Although large international registries of AFD patients exist, these do not systematically collect data that would allow the population to be screened for depression. The RADAR report (2005) analysed data from 211 patients in the Fabry Registry (which at the time contained data on 1863 patients) who had had an assessment and found depression in 31% (25/81) of females and 21% (27/130) of males.

Depression is often unrecognized in the general population: 50% of cases in the UK are not recognized in primary care (NHS Centre for Reviews and Dissemination 2002). It is also likely to be underdiagnosed in patients with AFD. This is important because early and vigorous intervention for depression improves outcome (Cross 2004; Katon and Ciechanowski 2002), decreases morbidity and mortality (Polsky et al 2005) and enhances social and economic wellbeing (WHO Health Evidence Network 2004) for the individual and the family (WHO 2001).

The objective of our study was to determine the prevalence of depression in adult patients with AFD in the United Kingdom and to identify factors associated with depression in this patient group.

Methods

A fixed, cross-sectional design with self-administered questionnaires was used. The protocol was reviewed and approved by the South East Multi-Centre Research Ethics Committee.

Patient sample and recruitment

Every adult patient with AFD attending the four designated lysosomal storage disorder centres in the UK between September and October 2006 was invited to participate. Five individuals with a current diagnosis of severe depression were excluded as it was felt that participation in the study might exacerbate their depressive illness. Potential participants were allocated a confidential identification number and invited by postal pack to participate (n=296). A reminder pack was sent three weeks later to those who had not responded.

Depression questionnaire

The Centre for Epidemiological Studies – Depression scale (CES-D) is a widely used, self-reporting depression scale (Arean and Miranda 1997; Boisvert et al 2003; O'Rourke 2005). The scale, designed by Radloff (1977), is a screening instrument to detect depressive symptoms in unselected populations. The CES-D was used because it is widely available, readily acceptable to respondents and allows for comparison with studies looking at depression in other populations.

The CES-D has consistently strong internal consistency (Cronbach's alpha=0.63 for progressive renal disease, α=0.90 for MS patients) in medically ill populations due to the focus on cognitive and affective components of depression rather than physical manifestations (Devins et al 1988; Hann et al 1999).

The CES-D has 20 questions which cover the major components of depression. Participants were asked to score the frequency of occurrence of specific symptoms during the previous week on a four point scale. These were summed to yield a total score between zero and 60. Participants scoring more than 15 were classified as having 'depressive symptoms' (validated by DSM-IV criteria for depression (Radloff 1977; Verdier-Taillefer et al 2001)). We used the scoring algorithm proposed by Ettinger and colleagues (2004): score 0–14, few or no symptoms of depression; score 15–21, mild to moderate symptoms of depression; score >21, severe depression

Supplementary questionnaire

We developed a supplementary questionnaire to collect demographic and socio-economic data, to collect Fabry-specific information and to determine whether patients had ever had depression diagnosed or

treated. This questionnaire consisted of 19 closed questions identified through the literature. Review by metabolic specialists and clinical psychologists established face validity. The questionnaire is available as Electronic Supplementary Material.

Observer bias was minimized by using closed-response questions which were clearly coded and not personally identifiable. Good reliability (test–retest correlations r=0.888 to 1) was seen in five responders who replied in error to both the first and reminder mail-outs. Kappa analysis of intra-observer error fell into the range considered as 'excellent' (>0.75) by Robson (1993).

Statistical analysis

Data from the questionnaires were entered into the SPSS (version 14) statistics program. Analyses were conducted according to pre-constructed analytical plans. Nonparametric chi-squared analysis was used to assess the bivariate difference between 'depressed' and 'not depressed' populations. Multivariate analysis (logistic regression) was used to account for the effects of confounding factors and their interactions on the odds of being depressed (CES-D>15). Models were assessed for maximum prediction value (especially sensitivity), smallest −2 log likelihood, statistically significant Wald's goodness of fit variables and odds which were theoretically plausible.

Results

A total of 184 surveys were returned for analysis; a response rate of 62%. Of these respondents, three did not complete the CES-D.

Demographic characteristics of responders are shown in Table 1. Nonresponders were similar in age and sex (59% female, 47% aged between 18 and 35, 45% aged between 36 and 55) to responders. Participants were from all parts of the UK. The majority were married or living with a partner. Over half were in full-time or part-time employment, comparable to the male cohort reported by McDermot and colleagues (2001). When compared with the national population (Office for National Statistics 2004), significantly more participants reported unemployment due to sickness or disability (16% vs 4%).

The mean age of participants was 44±14 years (range 18–76), which is slightly older than that reported by the international Fabry registries (35.5±13 for males and 41.4±17.1 for females (Mehta et al 2004); 37±15 for males and 40±18 for females

Table 1 Demographic and Fabry-specific characteristics of responders (n=184). Mean±standard deviation, or frequency and (%) as appropriate

Age	44±14
	Range 18–76
Sex	
Male	74 (40%)
Female	110 (60%)
Employment	
In/seeking employment	108 (59%)
Retired	24 (13%)
Sick/disabled	30 (16%)
Full-time education	6 (3%)
Looking after home/family	14 (8%)
Relationship status	
Single	33 (18%)
Married/cohabitating	132 (72%)
Separated/divorced/widow	15 (8%)
Children	
No children	54 (29%)
At least one with Fabry	77 (42%)
Children without Fabry	35 (19%)
"Fabry symptoms interfere with my life"	
Not at all	35 (19%)
Slightly	52 (28%)
Moderately	26 (14%)
Quite a bit	50 (27%)
Extremely	17 (9%)
Length of time receiving ERT	
<1 year	25 (22%)
1–2 years	38 (32%)
>2 years	55 (46%)
"Treatment interferes with my life"	
Not at all	27 (23%)
Slightly	56 (47%)
Moderately	20 (17%)
Quite a bit	12 (10%)
Extremely	2 (2%)
Highest level of education	
GCSE or less (<16 years)	84 (46%)
A-Levels(age 18 years)	34 (19%)
Degree/postgraduate	59 (32%)
Income	
Living comfortably on income	67 (36%)
Coping on income	85 (46%)
Difficulty on current income	20 (11%)
Very difficult on current income	11 (6%)
Age at first Fabry symptoms	20±18
	Range 3–70
Additional Chronic Illnesses	49 (27%)
	Range 1–5
"Fabry symptom interferes with my life"	
Acroparaesthesia	103 (56%)
Angiokeratoma	32 (17%)
Abdominal	88 (48%)
Anhidrosis	71 (39%)
Cardiac	67 (36%)
Cerebrovascular	36 (20%)

Table 1 Continued

Renal	51 (28%)
Ophthalmological	29 (16%)
Receiving ERT	119 (65%)
Symptom response to ERT	
Much/somewhat better	62 (53%)
About the same	45 (38%)
Much/somewhat worse	5 (4%)

(RADAR 2005)). This is because the population studied here contains a high proportion of female heterozygotes, who tend to present later and live longer than hemizygote male AFD patients.

Twenty-seven per cent of respondents reported other, often multiple, chronic medical conditions unrelated to AFD. Predominantly these were allergies and asthma, but 7 (3.8%) had diabetes, 4 (2.2%) had epilepsy, 4 (2.2%) had had a diagnosis of cancer and 6 (3.3%) suffered from other painful conditions such as arthritis.

The average age at which participants experienced their first AFD symptoms was 20±18 years (range 3–70), which is similar to that seen in previous reports (Deegan et al 2006; Mehta et al 2004). More women (n=43; 39%) than men (n=17; 23%) did not recall their age at first AFD symptoms, perhaps reflecting less severely affected females.

With regard to disease symptoms, comparison with registry data (where signs and investigations form the data) is difficult as the questionnaire used here asked only about symptoms which have an 'affect on the life' of the participants. This may explain why, with the exception of abdominal complaints and cerebrovascular disease, all symptoms reported here are less frequent than described elsewhere.

The proportion of participants receiving ERT was similar to that reported from the registries (90% of males (n=65) and 48% of females (n=53)). Almost half the participants (46%) had been receiving ERT for over 2 years, with another 21% having started in the previous 12 months; 52% felt that their symptoms were 'much' or 'somewhat' improved as a result of ERT.

Prevalence of depression

CES-D scores are shown in Fig. 1. Scores ranged from 0 to 51 out of a possible 60, with a mean of 16.2 (SD 12.75). The proportion of participants who demonstrated clinically significant depression was 46% (n=83). Of these, 28% (n=50) had a score suggesting severe clinical depression (score>21). The actual prevalence of depression is likely to be higher than this as five patients with known severe depression were excluded.

Figure 2 shows the proportion of under-diagnosis based on CES-D scores. Only 10% (n=18) of respondents had a current diagnosis of depression, representing just 22% of those with a CES-D score above 15 (n=83). Of the patients with positive depression scores, 12 out of

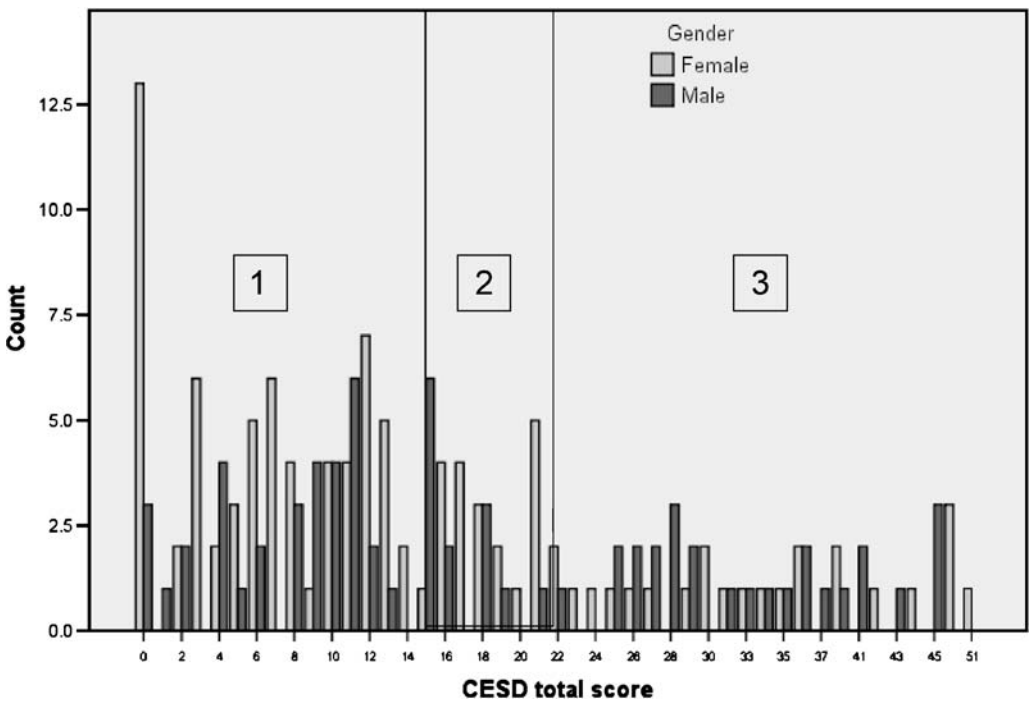

Fig. 1 Distribution of CES-D scores. 1: CES-D 0–15, No symptoms of depression; 54%. 2: CES-D 16–21, Symptoms of mild-moderate depression; 18%. 3: CES-D>21, Symptoms of severe depression; 28%

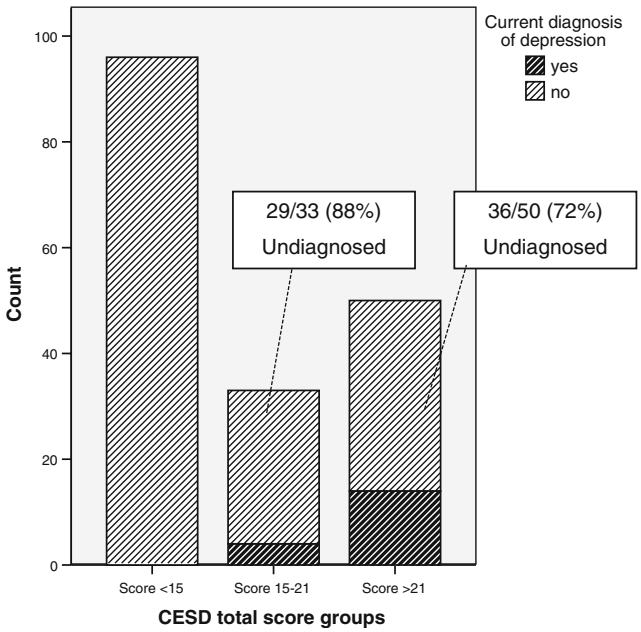

Fig. 2 Proportion diagnosed with depression based on CES-D scores

44 women (27%) and 6 of 39 men (15%) men knew themselves to be depressed.

As illustrated in Fig. 3, antidepressant medication was taken by 18 respondents. Of these, 10 had a 'severe' depression score, 5 had 'mild-moderate' depression and 3 were not depressed according to both their current diagnosis and the CES-D score (possibly reflecting a positive response to therapy). More women were taking antidepressant medication (13/18).

Four individuals had a current diagnosis and received both antidepressant medication and CBT. Their CES-D scores ranged from 21 to 49.

Eight participants had attended psychotherapy over the previous 6 months, five of whom were currently diagnosed with depression. Seven had CES-D scores indicating depression and the eighth had a history of depression but a CES-D score of 14 at the time of assessment. Five of the eight receiving CBT were women.

Factors associated with depression in Fabry disease

The differences between those depressed and not depressed, as well as the odds of being depressed, are shown in Table 2.

Depression in AFD was significantly associated with many of the same factors as in the general population (refer to Hamilton 2006). There were significant associations with economic and relationship status. Being married, or living with a partner, rather than single significantly decreased the odds of current depression. Those who were divorced, widowed or separated had an average twofold increase in their odds of being depressed compared with those who were single. Individuals reporting current financial difficulty also had an increased probability of depression.

Those participants who reported at least one medical condition in addition to AFD were four times more likely to experience depression than those with no morbidity. The extent to which the participants' Fabry-related symptoms 'interfered with life' showed a strong direct relationship with their depression scores. Those with anhidrosis or acroparaesthesiae had twofold to threefold increased odds of being depressed.

Age was not a predictor of depression in this AFD population. AFD also does not follow gender norms in relation to depression. In the general population, females are twice as likely to suffer from symptoms of depression as males (Hamilton 2006). In AFD, males' mean CES-D score (18.3±12.8) was higher than

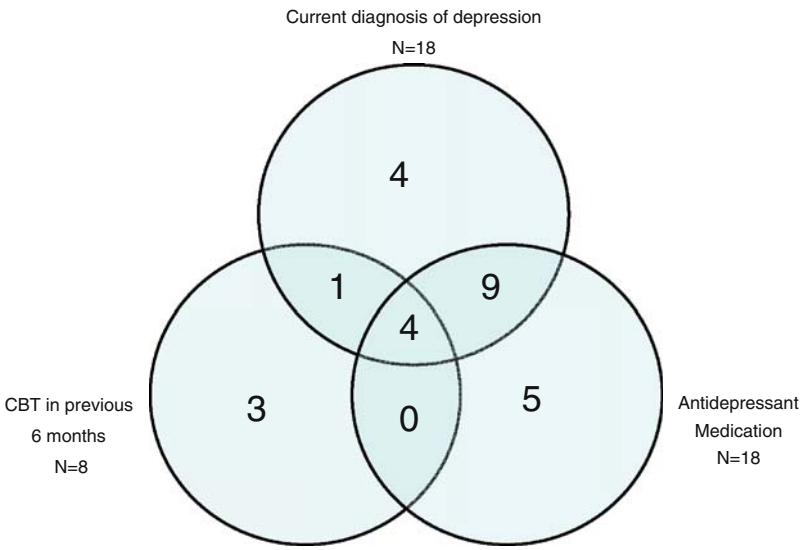

Fig. 3 Proportion diagnosed and/or receiving antidepressant medication and/or cognitive behavioural therapy

Table 2 Variables associated with depression in AFD

	CES-D<15[a]	CES-D>15[a]	Bivariate chi-square[b]	Logistic regression[c]
			χ^2 (df) p	Odds of CES-D>15 (95% CI)
Age			1.553 (3) $p=0.670$	
18–35 years	30 (59%)	21 (41%)		
36–55 years	44 (52%)	41 (48%)		
56-oldest	23 (52%)	21 (48%)		
Sex			3.134 (1) $p=0.077$	
Male	33 (46%)	39 (54%)		
Female	64 (59%)	44 (40%)		
Relationship status			7.932 (2) $p=0.019$*	
Single	13 (42%)	18 (58%)		(reference)
Married/cohabitating	78 (60%)	53 (40%)		0.36 (0.12, 1.07)
Separated/divorced/widowed	4 (27%)	11 (73%)		1.93 (0.36, 10.29)
Highest level of education			1.830 (2) $p=0.400$	
GCSE or less	42 (51%)	40 (49%)		
A-Levels or equivalent	16 (47%)	18 (53%)		
Degree/postgraduate	35 (60%)	23 (40%)		
Employment			14.065 (2) $p=0.001$**	
Employed/ful-time student	68 (62%)	40 (37%)		
Retired	14 (64%)	8 (36%)		
Unemployed/sick/disabled	16 (32%)	34 (68%)		
Income			14.773 (1) $p=0.000$**	
Comfortable/Coping	90 (60%)	59 (40%)		(reference)
Difficult/very difficult on income	7 (23%)	24 (77%)		2.34 (0.73, 7.54)
Another chronic illness			3.751 (1) $p=0.053$	
At least one other chronic Illness	22 (45%)	27 (55%)		4.14 (1.64, 10.41)
No other chronic illness	74 (61%)	47 (39%)		(reference)
Participants' children			0.000 (1) $p=0.991$	
No children/children without Fabry	48 (55%)	39 (45%)		
At least one child with Fabry	42 (55%)	34 (45%)		
Fabry symptoms interfere with life			40.972 (4) $p=0.000$**	
Not at all	29 (85%)	5 (15%)		(reference)
Slightly	36 (71%)	15 (29%)		2.78 (0.83, 9.26)
Moderately	13 (50%)	13 (50%)		6.73 (1.63, 27.74)
Quite a bit	14 (29%)	35 (71%)		16.72 (4.74, 58.98)
Extremely	3 (18%)	14 (82%)		46.59 (6.90, 315)
Acroparesthesia			19.790 (1) $p=.000$**	
Yes	41 (40%)	62 (60%)		3.03 (1.43, 6.41)[d]
No	57 (73%)	21 (27%)		(reference)
Angiokeratoma			6.119 (1) $p=0.013$*	
Yes	11 (34%)	21 (66%)		
No	87 (58%)	62 (42%)		
Abdominal			12.082 (1) $p=.0001$**	
Yes	36 (41%)	52 (59%)		
No	62 (67%)	31 (33%)		
Anhidrosis			16.866 (1) $p=0.000$**	
Yes	25 (35%)	46 (65%)		2.67 (1.27, 5.63)[d]
No	73 (66%)	37 (34%)		(reference)
Cardiac			5.746 (1) $p=0.017$*	
Yes	28 (42%)	38 (58%)		
No	70 (60%)	45 (40%)		
Cerebrovascula			3.496 (1) $p=0.062$	
Yes	14 (40%)	21 (60%)		
No	84 (58%)	62 (42%)		

Table 2 Continued

	CES-D<15[a]	CES-D>15[a]	Bivariate chi-square[b]	Logistic regression[c]
			χ^2 (df) p	Odds of CES-D>15 (95% CI)
Renal			3.465 (1) $p=0.063$	
Yes	22 (43%)	29 (57%)		
No	76 (59%)	54 (41%)		
Enzyme replacement therapy			5.408 (1) $p=0.020$*	
On ERT	57 (48%)	61 (52%)		
Not on ERT	40 (67%)	20 (33%)		
Length of time receiving ERT			10.791 (5) $p=0.056$	
<6 months	3 (38%)	5 (62%)		
6–12 months	10 (59%)	7 (41%)		
12–18 months	17 (63%)	10 (37%)		
18–24 months	5 (50%)	5 (50%)		
>2years	22 (40%)	33 (60%)		
Symptom response to ERT			191 (2) $p=0.909$	
Worse	2 (40%)	3 (60%)		
Same	22 (49%)	23 (51%)		
Improved	28 (46%)	33 (54%)		

[a] Frequency and (%).
[b] Bi-variate analysis: chi-square statistic, (degrees of freedom), p-value statistically significant at 0.001** and 0.05*.
[c] Logistic regression: odds of being depressed in comparison to reference group based on final model predicting 74.1% (76.6% CES-D +ve; 70.8% CES-D −ve).
[d] Logistic regression: a second logistic regression model entered individual symptoms, replacing the summary symptom question.

females' (14.9±12.7), although the difference was not statistically significant (Mann U, $z=-1.866$, $p=0.062$). Male patients also reported more symptoms of severe depression than females (36% and 22%, respectively), and were more affected by symptoms of AFD with 40% of 'severely depressed' males reporting 'extreme' effects of symptoms on their life as compared to 8.3% of 'severely depressed' females. Females, on the other hand, were more likely to report no symptoms of depression than males (12% of females had a CES-D score of 0 as opposed to 4% of males).

Discussion

This study is the largest survey of depression in patients with AFD. Previous studies have been greatly limited by small sample sizes (Hoffmann 2006). We found a high prevalence of symptoms of depression in this population. The probability of suffering from depression was strongly related to the degree to which symptoms interfered with everyday life. Our results also suggest that depression is both under-diagnosed and under-treated in these patients.

Taking into account the published specificity of 87.6% for the CES-D (Beekman et al 1997), the prevalence of depression in this population of patients with AFD is in the region of 43% (95% CI 42, 44). This is similar to the level of depression reported by Carson and colleagues (2003) in a study of neurological outpatients (40% depression rate), but appreciably higher than the rates of 11–25% depression reported in patients with heart failure (O'Conner and Joynt 2004). Patients with chronic pain (Ohayon 2004) have a higher prevalence of major depression than this AFD cohort (30–54% major depression), which is comparable to the 60% who reported acroparaesthesiae and have a CES-D depression score.

The multifactorial nature of both depression and AFD makes the determination of cause and effect relationships challenging. Previous studies of depression in AFD populations have been unable to perform multivariate analysis owing to small sample sizes. Logistic regression analysis identified four variables which identify patients at increased risk for depression. Three of these also predict depression in the general population: relationship status; financial status; and additional chronic illnesses. The strongest predictor was the degree to which symptoms of AFD interfered with a patient's life. Of AFD symptoms, acroparaesthesiae and anhidrosis led to the greatest increase in the odds of depression. These same symptoms were

reported by Gold and colleagues (2002) to have the greatest negative impact on quality on life.

The direct relationship between pain and depression emphasizes the importance of adequate analgesia for AFD patients. Adequate pain relief may lead to improvements in mood (Leo 2005). Liston and colleagues (1973) reported a 26-year-old man with severe acroparaesthesiae and psychotic depression. His pain responded to treatment with phenoxybenzamine, associated with a concomitant improvement in his mental state.

Additional factors such as delay in diagnosis, absence of social support networks, course of disease, current medications and other psychiatric diagnoses were not explored within this study but may also influence prevalence of depression in AFD adults.

No statistically significant difference was observed in the rate of depression between participants who had affected children and those who did not. However, the significant impact of the hereditary nature of AFD, as reported by Sadek and colleagues (2004), should not be underestimated. Anecdotal experience indicates this issue causes considerable anguish for some individuals, both male and female. A significant relationship with depression might have been detected if we had enquired about the severity of symptoms suffered by any affected children.

Despite the fact that depression is common and relatively easy to diagnose, 50% of cases are not recognized in primary care in the UK (NHS Centre for Reviews and Dissemination 2002). Even fewer receive treatment (20% medication, 3% cognitive therapy (The Depression Report, London School of Economics 2006)). When depression is associated with medical conditions, the diagnosis may be neglected as physicians concentrate on the primary illness (Hamilton 2006). This seems to be the case in AFD: within the UK AFD population, 88% of those whose CES-D scores indicated mild-moderate depression and 72% of those with severe depression scores had not been diagnosed.

This under-diagnosis may reflect the fact that depression can be seen as a predictable consequence or 'symptom' of AFD. It is, however, an important diagnosis to recognize as depression has severe consequences and can be treated. Patients whose depression is associated with chronic medical conditions can cope more effectively with their illness and symptoms if their depression is treated (Katon and Ciechanowski 2002). Conversely, if undiagnosed, depression can aggravate chronic physical conditions by increasing the severity of complications (Katon 2003; Polsky et al 2005), especially pain intensity and disability (Dersh et al 2002). Additionally, depression adversely impacts on self-management of the chronic illness by its adverse effects on memory, energy, sense of wellbeing, and interpersonal interactions (Katon and Ciechanowski 2002).

A disturbing consequence of depression is death by suicide. Suicide is three times more common in men than in women (Office for National Statistics 2007). Three UK AFD adults in the past year are known to have attempted suicide, one resulting in death. All three were men severely affected by their AFD symptoms and known to have depression. Early identification of depressive disorders (Thomas and Morris 2003) and compliance with treatment (National Institute for Mental Health in England 2006) can reduce the risk of suicide.

Physicians caring for AFD patients need to recognize and treat depression. When a patient is reporting symptoms which limit their everyday activities, they should be fully assessed for depression.

If scale utility specific to the AFD population were established it might be used as a convenient, easily administered, robust psychometric scale which could readily identify patients requiring a full diagnostic assessment. Psychiatric interviews with individuals indicating depression would add important depth to the knowledge of depression in AFD adults.

In this study we found that these patients have a depression rate which is higher than that of the general population and higher than that previously reported. These results are unlikely to be unique to the UK population. People caring for AFD patients should maintain a high degree of clinical suspicion for depression.

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