Depression: The Hidden Problem in Fabry Disease

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Abstract

Fabry disease (FD) is an X-linked disorder of glycosphingolipids caused by mutations of the GLA gene. The classical form presents with neuropathic pain and gastrointestinal complaints since childhood or adolescence and progressing into adulthood with ischemic stroke, cardiac dysfunction, and chronic kidney disease. Depression seems to be a frequent complication of FD but its frequently underdiagnosed and undertreated. Comorbid depression in different chronic diseases has been associated with an overall increase in disease burden and medical costs, impairment in activities of daily living, and impact on self-care and treatment adherence. In addition, a clear association between pain and depression has been observed in FD patients and appears to have an unequivocal neurobiological matrix. The aim of this review is to provide an overview of the literature on depression in patients with FD and to highlight some of the emerging issues on this topic. Further research to improve detection and to develop effective treatments for depression in this population is promptly needed.

Keywords: Fabry disease, depression, X-linked disorders, lysosomal storage diseases.

Fabry disease (FD), an X-linked disorder of glycosphingolipids caused by mutations of the GLA gene at Xq22.1 coding for α-galactosidase A, leads to dysfunction of many cell types resulting in a systemic vasculopathy. This abnormality affects the conversion of globotriaosylceramide (Gb3) to lactosylceramide with progressive multisystemic intracellular accumulation of glycosphingolipids, especially Gb3 [1,2]. These processes trigger inflammation and fibrosis in the vascular endothelium and generally result in multiorgan dysfunction [3]. The classical form of FD begins with neuropathic pain and gastrointestinal complaints during childhood or adolescence, complicated in adulthood with ischemic stroke, cardiac dysfunction, and chronic kidney disease [1]. Neurologic manifestations in FD are hallmarks of the disorder both in children and adults and include neuropathic pain, neuro-otological manifestations, stroke, and asymptomatic brain lesions [2,4]. Moreover, patients with FD report significantly worse scores than the general population on measures of both depression and anxiety [5,6].

The first evidence pointing toward a psychiatric involvement in patients with FD came from case reports that acknowledged the presence of personality changes or features of paranoid schizophrenia in FD individuals more than 50 years ago calling attention to the problem of depression in FD [7–9]. However, no particular interpretation regarding the etiology of these symptoms was speculated at that moment and it is currently still unclear whether depression in FD may arise from difficulties in coping with the severe and variable symptoms of the disease such as pain or cerebrovascular disease or as a direct pathological consequence of the disease *per se* [5,10].

Depression is a serious health condition that can significantly affect a person's occupational and/or educational performance as well as impact their familial or interpersonal relationships. At its worse, depression may lead to suicide, currently the second leading cause of death in adolescents and younger adults (15-29 years) [11]. Moreover, there is significant evidence indicating that depression in patients with different chronic medical illnesses is associated with a general increase in symptom burden, impairment in activities of daily living, an increase in medical costs as well as an impact on self-care and adherence to treatments [12]. Lastly, as has been widely observed in the general population, depression in FD is largely underrecognized [13],[14]. This review

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aims to provide a brief overview of depression in patients with FD. We highlight the frequency and the most important factors associated with depression, describe the neurobiology of the relationship between pain and depression, as well as the strengths and limitations of the different scales used to ascertain depression in FD and review treatment strategies. Furthermore, we address research priorities concerning future studies.

Material and Methods

A structured literature search was performed in September 2020 by the authors using PubMed and Embase. The main inclusion criterion was: any study or review published from 1962 onwards that provided detail on diagnosis, associated disorders and management of depression in Fabry disease. Individual case reports were excluded. Keywords used in the search strategy included the following MeSH terms: "Fabry Disease" AND ("depression" OR "psychiatry" OR "psychology" OR "pain" OR "quality of life"). Additional reports were identified by screening the reference lists of already included manuscripts.

Results

Frequency of depression in FD

The first study to assess the prevalence of psychiatric disorders in patients with FD was performed by the National Institutes of Health. This study retrospectively analysed the records of 33 patients followed from 1965 to 1990 and identified not only that 18% of this population presented psychiatric manifestations, but also that depression was the most frequent. Two patients from this group committed suicide which was hypothesized to be related to severe pain. The authors also reckoned that the prevalence of depression might have been probably underestimated since only those patients with a history of admission to a psychiatric facility were included, possibly disregarding less severe cases that may have been treated on an outpatient basis [15]. The largest survey assessing depression in FD, involving 184 patients, was performed in the United Kingdom and found that 46% of the respondents had clinically significant depression, with 28% suffering from severe depression. In contrast with the observations from the general population, men with FD showed a higher prevalence of severe depression than women (36% vs. 22%) [16]. Prevalence rates of depression in other studies have been largely variable, with estimates ranging from 18 to 100% [15,17]. (Table 1). These highly variable results are most likely due to the use of different measurement instruments and differences between study populations as reviewed in Table 1.

The frequency of depression in the classic versus the late-onset form of FD has not been evaluated. However, we believe that a longer duration of symptoms, with greater severity and the presence of pain, as can be observed in the classic form of FD, most likely predispose these patients to depression.

Finally, the only study investigating the psychological manifestations of FD exclusively on children (aged between 6 and 18 years) found that 21% of them reported symptoms compatible with clinical depression [18]. A summary of the most relevant studies analysing depression in FD patients can be found in Table 1.

Factors associated with depression in Fabry disease

Like in most chronic diseases, in particular those directly affecting the brain, it has been difficult to disentangle whether depression on FD arises from either a non-specific effect of a chronic illness or to difficulties in coping with the severe and variable symptoms associated with this disease, particularly neuropathic pain or stroke [5].

Most studies analysing depression in FD have linked its occurrence to both disease-specific and non-specific factors (see Table 2) [19]. Among the former, neuropathic pain has been independently associated with depressive symptoms in patients with FD [5],[16]. The evidence connecting pain and depressive symptoms has long been observed in many chronic pain syndromes. In fact, it has been estimated that 85% of those experiencing chronic pain may present severe depression. There is also evidence indicating that each condition can facilitate the development of the other [20]. This bidirectional relation has been specifically observed in FD patients, in whom improvement of depressive symptoms through counselling interventions may lead to a reduction of reported pain [21]. Similarly, depressive symptoms are expected to improve with adequate treatment of pain, reinforcing the complex interaction between the neurobiology of both disorders (see below) [22]. Moreover, Cole et al identified that life interference due to disease symptoms was the strongest predictor for the development of depression and psychiatric disorders and that severe painful neuropathy, pain crises and anhidrosis were the most significant FD symptoms driving this association [16]. On the other hand, the relationship between depression and cerebrovascular disease in FD has been controversial. This association was suggested by older studies but was not demonstrated in more recent investigations [23]. In a Dutch study including 81 FD patients, no relation was found between stroke or the Fazekas score for white matter lesions and depressive symptoms, assessed by the Center for Epidemiological Studies Depression Scale (CES-D) in two linear regression models [19]. These results are in line with a previous German study that did not find any association between depressive symptoms and neuroimaging parameters. The authors suggested that, while microangiopathic lesions in FD affect predominantly the periventricular regions, the typical lesions observed in late-onset or organic depression involve most frequently the subcortical frontal white matter [24].

Fabry disease patients present marked hippocampal atrophy on brain MRI, independent of the degree of involvement of the white matter or other brain regions [25]. This finding has been considered as an in vivo surrogate of neuronal involvement in

Table 1. Studies addressing depression in Fabry disease.

Author	N	Mean age (years)	Gender (%)	Mean time since diagnosis (years)	Depression prevalence (%)	Scale used	Pain prevalence (%)	Other FD manifestations (%)	Patients on ERT (%)	Treatment with antidepressants (N)
Grewal et al. (1993)	33	29	M (100)	NS	18	Psychiatric evaluation	100	Stroke (33)	NS	NS
MacDermot et al. (2001) [53]	60	44	F (100)	15	33	Mc Gill Q	80	Angiokeratoma (35) Hypohidrosis (33)	NS	NS
Sadek et al. (2004)	4	49	F (100)	10	100	HAM-D	75	Cardiac (25) Hearing loss (25)	NS	NS
Cole et al. (2007)	184	44	M (74) F (26)	20	46	CES-D	80	Anhidrosis (30)	65	18
Crosbie et al. (2009) [54]	28	25	M (57) F (43)	25	63	MMPI-2	72	Anhidrosis (92)	18	None
Segal et al. (2010) [55]	16	29	F (56) M (44)	NS	63	SADS and K-SADS	100	Cardiac (19) Renal (50) Angiokeratoma (50)	NS	NS
Schermuly et al. (2011)	25	36	F (60) M (40)	NS	60	HAM-D	80	Cardiac (80) Renal (80) Stroke (20)	20	NS
Sigmundsdottir et al. (2014)	17	47	M (70) F (30)	NS	41	DASS-21	100	Renal (21) Stroke (33)	9	None
Lelieveld et al. (2015)	14	47	F (71) M (29)	NS	21	HAM-D	NS	Cardiac (57) Renal (57) Stroke (21)	10	4
Bugescu et al. (2016)	24	12	F (58) M (42)	NS	21	CDI-2	45	Fatigue (70) Gastrointestinal (62) Exercise intolerance (45)	7	None
Ali et al (2018)	10	42	F (80) M (20)	NS	100	ASEBA	NS	NS	7	6
Rosa Neto et al. (2019) [56]	37	42	M (43) F (57)	NS	56	HAM-D	70	NS	22	22
Körver et al. (2020)	76	44	F (66) M (34)	NS	38	CES-D	75	Cardiac (55) Renal (13) Stroke (11)	45	7

FD: Fabry disease, ERT: Enzyme replacement therapy, NS: Not specified, M: Males, F: Females, Mc Gill Q: Mc Gill questionnaire short form, HAM-D: Hamilton depression rating scale, CES-D: Center for Epidemiological Studies Depression Scale, MMPI-2: Minnesota Multiphasic Personality Inventory, SADS: Schedule for Affective Disorders and Schizophrenia, K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version. DASS-21: Depression Anxiety Scale Score, CDI-2: Children's Depression Inventory Second Edition, ASEBA: Achenbach System of Empirically Based Assessment

Table 2. Factors associated with depression in patients with Fabry disease.

Disease-specific	Non-specific
Pain	Marital status
Other symptoms (i.e., anhidrosis)	Economic problems
Severity of organ complications	Lack of social networks
Cerebrovascular disease	Life interference due to FD
	Perceived health status
	Concerns regarding future
	Maladaptive coping mechanisms

FD, and hippocampal atrophy was also described in association with both neuropathic pain and major depression in the non-FD population [26],[27]. Nevertheless, studies performed up to this moment failed to show any association between hippocampal decline in FD patients and either pain or depression [25,28].

Non-disease-specific factors associated with depression in FD include: being single, divorced/widowed, having financial difficulties and perceiving a lack of social support [16],[29]. Additional associated conditions included a negative perceived health status, an increased severity of the disease, and the presence of subjective concerns regarding the future, heritability, and social stigma. Recently, coping mechanisms have been identified as probable mediators of either an adaptive or maladaptive response to the challenge of facing a chronic disease. As with other chronic conditions, FD patients exhibiting an avoidant and brooding coping style, as opposed to a more positive and problem-solving approach, more frequently present depressive symptoms [19]. Moreover, coping mechanisms might also be related to depression due to its influence on pain experience [5]. Other features that may also predispose patients to chronic depression include time-dependent increase in disability and the awareness of their shortened lifespan [30].

Depression in children with FD is most likely explained by the psychological distress related to living with a chronic, progressive and painful illness [31]. The familial nature of the disease may also play a role as older children may become increasingly aware of the long-term consequences of FD via exposure to their parent's experiences [18].

Neurobiology of pain and depression in FD

The close relationship between neuropathic pain and depression is of utmost importance in FD and has a clear neurobiological matrix [32]. Pain is a complex sensation that includes emotional and behavioural components in addition to the classic sensory discrimination. In patients with the classic form of FD, neuropathic pain is frequent, occurs early, and is usually severe [33]. As part of its neurobiological complexity, pain activates several brain regions within the limbic system that overlap with areas processing emotional stimuli often affected in depression as well. This may lead to functional and structural alterations in the central nervous system. Neuroimaging studies have demonstrated that several areas, including the prefrontal cortex, insula, amygdala, hippocampus, and cingulum are functionally or structurally abnormal in both chronic pain and depressive states [32,34,35]. Patients with depression develop the main features of inflammation, including elevations in cytokines both in blood and cerebrospinal fluid, as well as an increase in serum acute-phase proteins, chemokines, and adhesion molecules [32,36]. A similar pattern of this proinflammatory state has been now recognized in both FD and in peripheral nerve injury [37,38].

The presence of pain may delay the recognition and therefore the treatment of depression. On the contrary, the resolution of pain doubles the remission rate of depression [39,40]. Moreover, during the treatment of a depressive disorder, pain may act as a major obstacle to achieve remission and a risk factor for relapse, decreasing the chances for an optimal outcome [41].

Instruments to screen for depression in patients with Fabry Disease

Several questionnaires to screen for depression are available for their use in both the general population and in individuals with chronic diseases. These instruments vary regarding their length, ease of use, availability, sensitivity and specificity, but are mostly composed of standardized questions assessing for depression symptoms and their severity [42]. Nevertheless, these tests are not diagnostic of depression and their use in clinical practice should always be considered as screening tools and part of a two-stage assessment process. Patients presenting with scores above the cut-off point should be further assessed by mental health professionals to establish a definite diagnosis of depression [43].

The most commonly used depression rating scales in the medically ill are the Patient Health Questionnaire 9 (PHQ-9), the Center for Epidemiologic Studies Depression Scale (CES-D), the Beck Depression Inventory-II (BDI-II), and the Hospital Anxiety and Depression Scale (HADS). There is some concern that the HADS and CES-D may capture non-specific psychological symptoms of distress, thus lowering their specificity for detecting depression in individuals with chronic diseases [43].

In patients with FD, different screening instruments for measuring depressive symptoms have been used (see Table 1). However, none of these tests have been specifically validated for this population. The most frequently used tests so far are the Hamilton Rating Scale for Depression (HAM-D) and the CES-D [44,45]. The HAM-D has been repeatedly criticized for its high sensitivity to somatic symptoms of depression and certain studies suggest this instrument may overestimate depression rates when used in patients with chronic diseases [46,47]. The somatic symptoms of depression refer to a diverse group of physical symptoms that may frequently characterize depressive mood, such as dysesthesia, pain, sleep disturbances, fatigue, changes of appetite and weight, among others [48]. These symptoms may be simultaneously attributable to both medical conditions and depression, leading in some cases to diagnostic confusion [49].

The PHQ-9 scale, a freely available and relatively brief tool, mapping the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria, has become an increasingly used instrument for screening depression in patients with different chronic diseases [50]. The growing use of this tool may warrant the assessment of its psychometric characteristics in future studies among patients with Fabry disease and to compare its results with formal psychiatric evaluation.

Treatment of depression in patients with Fabry disease

There is insufficient evidence linking enzyme replacement therapy to an improvement or prevention of depressive symptoms in adults [19]. However, there is some evidence that children receiving ERT reported clinically meaningful fewer symptoms of inattention, stronger overall adaptive functioning and lower mean depression scores approaching significance than their counterparts not receiving ERT [18].

With regard to the specific treatment of depression in adult FD patients, at the moment, there are no randomized-controlled trials addressing the efficacy of antidepressants in this population. A small study following FD patients for a period of up to eight years found a non-significant decrease in clinically relevant depressive symptoms from 50% at baseline to 21% at last follow-up. This decline could have been related to the initiation of antidepressant therapy after study enrolment. Unfortunately, there was no information available regarding which specific antidepressants were selected [28]. Due to the lack of specific FD data, pharmacological treatment of depression at this moment, does not differ from that of the general population. However, when selecting antidepressants in FD patients, particular consideration has to be given to the severity of organ complications (in particular brain, heart and kidney), other comorbidities and potential drug-drug interactions. Moreover, considering the frequent association of depression and chronic neuropathic pain in FD patients, certain antidepressants, such as the dual serotonin and noradrenaline reuptake inhibitors (especially duloxetine), efficacious for both depression and pain, exhibit an interesting profile and may allow to treat both disorders with a single medication [51].

Concerning psychological interventions, a recent study assessing changes in depressive symptoms after a 1-year follow-up found no difference when comparing CES-D scores between patients that received a counselling intervention and those who did not [52]. On the contrary, a small study assessing the effects of a counselling intervention administered by a psychotherapist and utilizing cognitive-behavioural strategies and insight-oriented techniques tailored to each patient particular situation improved depression in FD patients for up to 6 months after concluding the intervention. Ratings of quality of life and subjective pain severity scales also improved [21].

Conclusion

Depression is a very frequent problem in patients with FD but it is often underdiagnosed and undertreated. Pain, a hallmark of FD, is closely associated to the development of depression. We believe all FD patients should be screened for depression and referred to a mental health specialist when appropriate. Prospective studies are necessary to validate the use of CES-D, BDI-II, and the HADS in patients with FD and compare their sensitivity and specificity. Future research priorities should include a comprehensive evaluation of the psychological impact of FD since childhood as well as controlled studies on the effect of disease-adapted psychological and psychopharmacological interventions tailored to these patients.

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