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Impact of ataxia aetiology on self-reported mental health, fatigue, cognition and ataxia symptom severity

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Abstract

Introduction It has been increasingly recognised that the impact of Ataxia extends beyond physical and motor symptomology. However, it is less known whether self-reported non-motor and ataxia symptom severity varies across ataxias of differing aetiology, which would have important implications for providing more targeted treatment.

Aim This study aimed to investigate the impact of ataxia aetiology (hereditary, acquired or idiopathic) on self-reported depression, anxiety, fatigue, cognitive deficits, and ataxia symptom severity. Comparisons were also made between the ataxia sample as a whole and a neurologically healthy control group.

Method Responses were collected using a cross-sectional online survey to recruit a national UK sample of people with ataxia.

Results The study recruited 110 participants with ataxia (hereditary = 51, acquired = 16, idiopathic = 43) and 32 healthy controls. No significant differences were found across study variables for different causes of ataxia. However, participants with ataxia did report significantly higher levels of depression, anxiety, fatigue, cognitive deficits, and ataxia symptom severity compared to healthy controls.

Conclusion This study found that participants with ataxia self-reported increased non-motor symptoms compared to healthy controls, which was a generally homogenous experience across different causes of ataxia. There was also considerable comorbidity of symptoms which requires further exploration. This study highlights the need for early assessment and intervention to address these non-motor symptoms in ataxia populations.

Keywords Ataxia · Depression · Anxiety · Fatigue · Cognition

1 Introduction

Ataxia refers to a group of rare neurological conditions which impact coordination, vision, balance and speech [17]. However, there is growing evidence that the impact of ataxia extends beyond physical symptomology [19]. Anxiety and depression have been found to be disproportionately high for people with ataxia compared to the general population [5, 13], which has been linked to increased ataxia symptom severity [18]. Reports of fatigue are also significantly greater for individuals with ataxia compared to healthy controls [22], which appear to be influenced by ataxia symptom severity, duration of diagnosis, and depression [3, 30]. A range of potential deficits in cognition have been recognised in ataxia which are characteristic of a 'cerebellar cognitive affective syndrome' (CCAS) highlighting the role of the cerebellum in modulating cognition and affect [1]. There is also a high prevalence of comorbid neuropsychiatric symptomology (e.g.

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depression, anxiety, disinhibition) which contributes to the experience of ataxia, although it is often under-diagnosed and requires further research [12, 16].

Ataxia itself is not considered a specific diagnosis and typically warrants further investigation to establish a specific cause, which is commonly divided into hereditary and acquired [7]. A further distinction is often made for an idiopathic (or sporadic) ataxia in which the cause is unknown [14]. Although these categorisations can be heterogenous (e.g. an idiopathic ataxia may have a hereditary cause which has yet to be identified), this distinction is important for capturing patient perspectives. For instance, interviewed patients who were given a 'definitive' hereditary diagnosis of ataxia had greater satisfaction compared to those with an idiopathic ataxia, which provoked fear and criticisms of medical competence [6]. However, it is less clear how different causes of ataxia are related to non-motor symptomology (e.g. depression, anxiety, fatigue) as most studies focus on a single cause using clinician-rated tools, which do not capture the patient perspective.

Until recently, there has not been a validated measure of ataxia severity which considers the patient's (self-reported) view [23]. This development has allowed self-reported ataxia severity ratings to be collected alongside other measures of non-motor symptomology to provide a more complete patient perspective, without the need for a clinical examination. This also supports online recruitment methods to gain a more representative national sample, rather than recruitment being confined to a single clinic/hospital which commonly occurs in ataxia research. There is further a need to better understand the suitability of commonly used psychiatric measures with ataxia populations due to criticisms that they may be too 'conservative' for capturing sub-clinical symptoms [16].

This study aimed to investigate the impact of ataxia aetiology (hereditary, acquired and idiopathic) on self-reported depression, anxiety, fatigue, cognitive deficits, and ataxia symptom severity. A neurologically healthy (no ataxia) control group was also included to aid comparisons. Supplementary analysis aimed to explore relationships between self-reported non-motor symptoms, ataxia symptom severity, and duration of diagnosis. A secondary aim of the study was to independently explore the internal consistency of the Patient-Reported Outcome Measure of Ataxia—Short Form and other psychometric measures, when administered in an online format with an ataxia sample.

2 Materials and methods

2.1 Participants and procedures

The study recruited 142 participants which included those with ataxia ($n = 110$) and healthy controls ($n = 32$). Participants were recruited nationwide in the UK using social media and advertisements from the charity Ataxia UK. All data was collected via an online survey which hosted the self-report measures. Informed consent was obtained for each participant prior to taking part. Participants were not eligible to take part if they were under 18 years of age, had another neurological condition, or were based outside the UK. Causes of 'acquired' ataxia were defined according to Klockgether [14] to include disorders in which ataxia was a predominant sign (e.g. alcoholic cerebellar degeneration, immune-mediated inflammation) rather than part of a complex syndrome (e.g. stroke, traumatic brain injury). Participants were entered into a prize draw for one of five vouchers as reimbursement for their time.

2.2 Materials

The Patient-Reported Outcome Measure of Ataxia—Short Form (PROM-Ataxia-SF; [23]) was used as a brief, self-report measure of ataxia symptom severity. This includes 10 items which are rated over the past two weeks. Items are divided into 'physical' and 'mental' dimensions which are rated on a scale from 0 (without any difficulty/never) to 4 (unable to do/always).

Depression was measured using the widely used Patient Health Questionnaire 9-Item Scale (PHQ-9; [15]) and anxiety using the Generalised Anxiety Disorder 7-Item Scale (GAD-7 [25],). These are both rated over the previous two weeks using a scale from 0 (not at all) to 3 (nearly every day).

Physical and mental fatigue was assessed using the 14-item Chalder Fatigue Scale (CFS; [4]). This is rated dichotomously using 0 (no) and 1 (yes). Participants with ataxia were asked to base their response on their experience compared to before being diagnosed with ataxia, whereas participants without ataxia were asked to respond based upon how they generally felt 'in this moment'. These instructions were informed by the Ataxia UK Ethics Board.

Frequency of self-reported cognitive deficits were measured using the 25-item Cognitive Failures Questionnaire (CFQ; [2]). This asks participants to rate the frequency of specific scenarios involving cognitive errors over the previous six months. Participants rate each scenario on a scale of 0 (never) to 4 (very often).

2.3 Statistical analysis

Statistical analysis was performed using SPSS 29.0 [10]. Internal consistency was explored using Cronbach's Alpha for each measure. As parametric assumptions were not met, a Mann–Whitney U test was undertaken to compare the ataxia group to the healthy control group across study variables. A further Kruskal–Wallis test compared study variables across each cause of ataxia with follow up pairwise comparisons. Significance values were adjusted using a Bonferroni correction for multiple tests. Bivariate Pearson's correlations were used to explore associations between ataxia symptom severity and the other study variables for the ataxia group only.

3 Results

3.1 Demographic and descriptive statistics

The study recruited 142 participants (51 male, 86 female, 3 non-binary, and 2 not specified). The ataxia group had an age range of 18 to 85 years ($Mdn = 59$, $M = 53.7$, $SD = 17.8$) and the healthy control group was 18 to 75 years ($Mdn = 47$, $M = 41.3$, $SD = 17.3$). There was a significant difference in age across the ataxia and healthy control groups using a Mann–Whitney U test, $U = 2626.00$, $p < 0.001$, $r = 0.36$.

The ataxia group were further divided into hereditary ($n = 51$; *Mdn* Age = 52, *M* age = 51.3, $SD = 14.6$), acquired ($n = 16$; *Mdn* Age = 54, *M* age = 51.5 $SD = 17$), and idiopathic ($n = 43$; *Mdn* Age = 71, *M* age = 66.4, $SD = 13.9$) ataxia. The ataxia sample showed a significant difference in age across groups using a Kruskal–Wallis test, $H(2) = 23.31$, $p < 0.001$. Pairwise comparisons found that the idiopathic ataxia group were significantly older compared to participants with hereditary ataxia ($p < 0.001$, $r = -0.44$) and acquired ataxia ($p = 0.07$, $r = -0.29$).

The ataxia groups did not differ with regard to the duration of time since ataxia diagnosis ($H(2) = 3.26$, $p = 0.196$), although there were differences found for age of diagnosis, $H(2) = 20.15$, $p < 0.001$. Participants with idiopathic ataxia were diagnosed at a significantly older age ($Mdn = 61$, $M = 57.79$, $SD = 19.38$) compared to those with hereditary ataxia ($Mdn = 40$, $M = 40.86$, $SD = 15.25$), $p < 0.001$, $r = -0.46$. Descriptive statistics for each variable by group (control, ataxia, ataxia cause) are displayed in Table 1.

3.2 Psychometrics

The psychometric properties of each measure were explored for the ataxia participants only ($n = 110$). The PROM-Ataxia-SF had excellent internal consistency ($\alpha = 0.904$) which would not have been further improved with item deletion. The GAD-7 ($\alpha = 0.906$) and CFQ ($\alpha = 0.941$) were also found to have excellent internal consistency, whereas the PHQ-9 ($\alpha = 0.874$) was considered to be good. The CFS was explored using both the 14-item and 11-item versions (see [4]). It was interesting to find that the 14-item version yielded better internal consistency for measuring fatigue in this ataxia sample ($\alpha = 0.815$) compared to using 11-items ($\alpha = 0.762$). Furthermore, it was found that deleting the 3 items relating to language and memory would have further improved the internal consistency of the measure for ataxia participants. The 14-item CFS was used for further analysis.

3.3 Ataxia and healthy control groups

A Mann–Whitney U test was initially used to compare all participants with ataxia (regardless of cause) with the healthy control group across study variables. Participants with ataxia reported significantly higher scores for anxiety ($U = 2591.50$, $p < 0.001$, $r = 0.34$), depression ($U = 2670.50$, $p < 0.001$, $r = 0.38$), fatigue ($U = 2934.00$, $p < 0.001$, $r = 0.54$), and cognitive deficits ($U = 2130.50$, $p = 0.046$, $r = 0.17$). Fatigue was found to have the largest effect size, followed by depression with a medium effect. Collectively this suggests that individuals with ataxia report significantly poorer psychological and cognitive functioning compared to healthy controls. The ataxia group also scored significantly higher than the healthy control group on the PROM-Ataxia-SF, $U = 3250.50$, $p < 0.001$, $r = 0.65$, with a large effect size.

Table 1 Descriptive Statistics for Study Variables for Healthy Control, Ataxia (all aetiologies combined), and Ataxia Aetiology Groups

Participant group	*n*	*M* age of diagnosis (*SD*)*	*M* duration of diagnosis (*SD*)*	Self-report measure	*M*	*SD*
No Ataxia (control)	32	–	–	GAD-7	3.47	3.55
				PHQ-9	4.53	3.38
				CFS	3.38	3.33
				CFQ	33.38	16.06
				PROM-Ataxia-SF	2.71	6.21
Ataxia (all aetiologies combined)	110	47.62 (19.40)	9.56 (9.50)	GAD-7	7.97	5.80
				PHQ-9	10.50	6.85
				CFS	9.09	3.48
				CFQ	40.84	18.88
				PROM-Ataxia-SF	23.35	9.45
Hereditary Ataxia	51	40.86 (15.25)	10.51 (8.89)	GAD-7	9.02	6.14
				PHQ-9	11.10	7.17
				CFS	8.55	3.66
				CFQ	40.53	19.27
				PROM-Ataxia-SF	22.84	10.16
Acquired Ataxia	16	42.13 (20.92)	9.33 (8.73)	GAD-7	8.75	6.15
				PHQ-9	10.19	6.83
				CFS	9.47	3.27
				CFQ	45.56	18.35
				PROM-Ataxia-SF	24.19	9.72
Idiopathic Ataxia	43	57.79 (19.38)	8.48 (10.53)	GAD-7	6.44	4.99
				PHQ-9	9.93	6.58
				CFS	9.59	3.31
				CFQ	39.44	18.79
				PROM-Ataxia-SF	23.65	8.63

*Age and duration since diagnosis in years

As significant differences in age were found between groups, this was explored further as a potential confounding variable using Quade's Test for non-parametric analysis of covariance. This demonstrated that whilst considering the influence of age, significant differences were still found for anxiety, $F(1,139) = 22.99$, $p < 0.001$, depression, $F(1,138) = 19.27$, $p < 0.001$, fatigue, $F(1,134) = 40.97$, $p < 0.001$, cognitive deficits, $F(1,137) = 5.946$, $p = 0.016$, and ataxia symptoms, $F(1,138) = 61.65$, $p < 0.001$, with higher scores for all variables in the ataxia group compared to healthy controls.

3.4 Ataxia cause

To compare study variables across causes of ataxia (hereditary, acquired, idiopathic), Kruskal–Wallis tests were performed. No significant differences across ataxia groups were found for anxiety ($H(2) = 4.245$, $p = 0.120$), depression ($H(2) = 0.478$, $p = 0.787$), fatigue ($H(2) = 2.249$, $p = 0.325$), cognitive deficits ($H(2) = 1.521$, $p = 0.467$), or ataxia symptom severity ($H(2) = 0.98$, $p = 0.952$). Therefore, participants appeared to report a homogenous experience of non-motor and ataxia-related symptomology regardless of the cause of ataxia.

3.5 Relationship between psychological, cognitive and ataxia-related factors

Bivariate Pearson's correlations explored associations between ataxia symptom severity, years since diagnosis, and the other study variables in participants with ataxia only (see Table 2). Variables were linear, normally distributed and contained no outliers. Ataxia symptom severity had a significant positive correlation with depression, $r(107) = 0.448$, $p < 0.001$, and fatigue, $r(103) = 0.383$, $p < 0.001$, with medium effect sizes. Significant positive correlations with smaller effect sizes were also found for ataxia symptom severity with cognitive dysfunction and anxiety. Anxiety, depression, fatigue and

Table 2 Correlations between study variables and duration of diagnosis for participants with Ataxia

	1	2	3	4	5	6
1. GAD-7	–					
2. PHQ-9	0.746***	–				
3. CFS	0.401***	0.534***	–			
4. CFQ	0.417***	0.418***	0.513***	–		
5. PROM-Ataxia-SF	0.208*	0.488***	0.406***	0.289***	–	
6. Duration of diagnosis (years)	− 0.045	− 0.055	0.42	0.97	0.247**	–

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

cognitive deficits were also significantly correlated with each other (see Table 2), highlighting that these constructs were highly related in people with ataxia. Duration of diagnosis revealed a positive correlation with ataxia symptom severity, $r(106) = 0.247$, $p = 0.010$, with longer time living with ataxia being associated with increased symptom severity. No other factors were associated with duration of diagnosis.

4 Discussion

This research aimed to investigate the impact of ataxia aetiology on self-reported depression, anxiety, fatigue, cognitive deficits, and ataxia symptom severity within a UK national sample. The study found no significant differences in these variables across different causes of ataxia. However, participants with ataxia regardless of aetiology, reported significantly higher levels of depression, fatigue, anxiety, cognitive deficits, and ataxia symptom severity compared to healthy controls. These findings reflect previous research which has shown depression, fatigue and cognitive dysfunction are elevated across different ataxia populations [5, 13, 18, 20, 22, 30], which can have a significant impact on quality-of-life due to the range of related physical and cognitive symptoms [11]. Therefore, the experience of non-motor and ataxia-related symptomology was generally homogenous across different causes of ataxia within the present study.

The ataxia group reported elevated scores on commonly used measures of anxiety and depression in which each of these questionnaires were found to have good to excellent internal consistency. Using recommended cut-offs for the GAD-7 and PHQ-9 [15, 25], the reported means for the ataxia group were above recommended clinical thresholds indicative of mild anxiety and moderate depression. This highlights the importance of early intervention at the point of diagnosis to reduce mental health problems [8]. It has been proposed that this may include improving self-efficacy, sense of control, and acceptance of ataxia-related difficulties [21].

Fatigue is a well-known symptom of ataxia in which a previous study reported that 70% of participants described fatigue as one of the three most disabling symptoms of ataxia [3]. The findings from the present study suggest that fatigue is experienced similarly across different causes of ataxia, which was considerably higher than the healthy control group with a large effect size. There were also significant correlations between fatigue, anxiety, depression, and cognitive deficits, highlighting the comorbidity of these symptoms for people with ataxia. This is consistent with previous research which has highlighted that three or more neuropsychiatric symptoms were present in over half of their ataxia cohort [16].

Ataxia severity was found to be significantly associated with greater fatigue, cognitive dysfunction, anxiety, depression and years since diagnosis. This could suggest that as the severity of ataxia symptoms increases, the risk of developing neuropsychiatric symptomology is also likely to increase, which has been previously highlighted for depression in spinocerebellar ataxia [18]. However, it is important to note that due to the use of correlational methods, we are unable to imply a causal relationship. Even so, it is important to highlight that these relationships exist for future studies. It is also acknowledged that the questionnaires used in the current study contained items measuring similar constructs (e.g. the CFS, PHQ-9 and PROM-Ataxia-SF all contain cognitive items), which may have increased the size of the correlations between these measures. Therefore, as suggested by other authors (e.g. [12]), it is important that new validated tools are developed to better detect and delineate the relationship between these constructs in ataxia populations.

The frequency of 'everyday' cognitive deficits was found to be elevated in the ataxia group compared to healthy controls, which is consistent with the view that ataxia results in recognised cognitive deficits [1]. However, it is important to

note that this finding was based upon subjective self-reports, rather than more objective performance-based measures (e.g. CCAS scale [9],). Furthermore, the acquired ataxia group which reported the highest mean score for cognitive difficulties, was limited by a small sample size which led to the analysis being underpowered. As a result, this may warrant further investigation using larger samples.

Prior to the development of the PROM-Ataxia measure, assessment of ataxia symptoms was limited to observations in clinic and rating scales administered by clinicians [23]. This study has found evidence of excellent internal consistency for the short-form of the PROM-Ataxia measure, which also found a significant difference between the ataxia and healthy control group. Considering this is a brief tool which could be administered online, it has potential for remote monitoring of ataxia symptomology for patients and supporting online recruitment for research. This is particularly advantageous considering the difficulties with recruiting patients with ataxia into trials and may mitigate some of the barriers such as the burden and costs of travel to clinics [27]. Due to the significant differences between participants with ataxia and healthy controls on the PROM-Ataxia-SF, it may also have a role in informing diagnosis. However, this will require further investigation to determine sensitivity and specificity, particularly when compared to other neurological conditions.

This study had several limitations which should be considered. The acquired ataxia group had a smaller sample size compared to other types, which may have been related to the exclusion criteria of having no other neurological condition (e.g. stroke). However, it was considered important to include this criterion to attribute self-reported symptoms as being primarily related to ataxia, rather than other neurological causes. The control group was also smaller than the ataxia group as a whole. As a result, targeted sampling may be needed for recruitment in similar studies. There was a significant age difference between the ataxia and healthy control group with the ataxia group being generally older, particularly for participants with idiopathic ataxia who were diagnosed in later life compared to hereditary ataxias. This was found to be comparable to previous studies of idiopathic ataxia [31], but could have implications for age-related changes in cognition and mobility [29]. Age has also been shown to negatively correlate with cognitive functioning in CCAS [26]. Future research evaluating the PROM-ataxia should explore the impact of such demographic factors on cognitive functioning across causes of ataxia.

Finally, it is important to note that ataxia diagnosis was not confirmed by a health professional and relied on self-report, which did not include detailing specific ataxia types and could lead to errors in classification. It was also not possible to correlate ataxia severity from the PROM-Ataxia-SF with other measures such as the Scale for the Assessment and Rating of Ataxia [24] or International Cooperative Ataxia Rating Scale [28]. As these tools are clinician-rated, this was beyond the scope of this online study which aimed to recruit a nationwide sample. Similarly, objective cognitive measures (e.g. CCAS scale [9],) were not used and therefore we were unable to explore the relationship between performance and cognitive items of the PROM-ataxia. Future studies may benefit from initially verifying ataxia diagnosis and cognitive functioning in clinic with established tools, then using the PROM-Ataxia for collecting follow-up data remotely using a longitudinal design to monitor symptoms over time.

5 Conclusion

In summary, this study aimed to investigate the impact of ataxia aetiology (hereditary, acquired, idiopathic) on self-reported depression, anxiety, fatigue, cognitive deficits, and ataxia symptom severity. No significant difference in non-motor or ataxia symptom severity was found across different causes of ataxia. However, participants with ataxia did report higher levels of depression, anxiety, fatigue, cognitive deficits, and ataxia symptom severity compared to healthy controls. Therefore, the experience of non-motor and ataxia-related symptomology was found to be generally homogenous across ataxia aetiologies within the present study. There was also considerable comorbidity of these symptoms which requires further exploration. This study highlights the need for early assessment and intervention to address non-motor symptoms in ataxia populations. Furthermore, promising psychometric evidence was found for the use of the PROM-Ataxia-SF as an online self-report measure, which may mitigate some of the recruitment barriers in ataxia research.

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Data availability Datasets can be accessed via the corresponding author.

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the University of Southampton Faculty Ethics Committee (ERGO 70322) and Ataxia UK to advertise the study. Informed consent was obtained from all participants to take part in the study.

Consent for publication Informed consent was obtained from all participants to publish their data in a journal or present at a conference.

Competing interests The authors declare no competing interests.

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