ORIGINAL ARTICLE

Neuropsychiatric Symptoms as a Reliable Phenomenology of Cerebellar Ataxia

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Abstract

While cerebellar ataxia (CA) is a neurodegenerative disease known for motor impairment, changes in mood have also been reported. A full account of neuropsychiatric symptomology in CA may guide improvements in treatment regimes, measure the presence and severity of sub-clinical neuropsychiatric disturbance symptomology in CA, and compare patient versus informant symptom recognition. Neuropsychiatric phenomena were gathered from CA patients with genetic and unknown etiologies and their informants (e.g., spouse or parent). Information was obtained from in-person interviews and the Center for Epidemiologic Studies Depression Scale. Responses were converted to the Neuropsychiatric Inventory-Questionnaire (NPI-Q) scores by consensus ratings. Patient NPI-Q scores were evaluated for symptom prevalence and severity relative to those obtained from healthy controls. Patient-informant NPI-Q score disagreements were evaluated. In this cohort, 95% of patients presented with at least one neuropsychiatric symptom and 51% of patients with three or more symptoms. The most common symptoms were anxiety, depression, nighttime behaviors (e.g., interrupted sleep), irritability, disinhibition, abnormal appetite, and agitation. The prevalence of these neuropsychiatric symptoms was uniform across patients with genetic versus unknown etiologies. Patient and informant symptom report disagreements reflected that patients noted sleep impairment and depression, while informants noted irritability and agitation. Neuropsychiatric disturbance is highly prevalent in patients with CA and contributes to the phenomenology of CA, regardless of etiology. Clinicians should monitor psychiatric health in their CA patients, considering that supplemental information from informants can help gauge the impact on family members and caregivers.

Keywords Ataxia · Cerebellar degeneration · Mood · Neuropsychiatric · Cerebellum

Introduction

Cerebellar ataxia (CA) is a neurodegenerative disease with a predominantly cerebellar focus [1]. The most prominent symptom in CA is motor impairment. CA patients typically report their first symptoms as changes in motor coordination, including gait disturbance, clumsiness, and dysarthria [2]. These initial challenges to motor function often progress over months and years to moderate or severe disability that requires assistance in daily domestic and professional tasks [3]. While therapeutic attention tends to focus on motor impairments, non-motor symptoms are also present in CA, aligning with findings that the cerebellum contributes to cognition, perception, and mood regulation [4–9]. Neuropsychiatric symptoms in CA are particularly relevant for consideration in the treatment of CA patients because they can interfere with everyday tasks, hinder disease management, and disrupt social and occupational functions.

Studies of neuropsychiatric state changes in CA are limited. A previous investigation of non-motor symptoms in CA reported that 77% of a CA patient cohort (24 of 31 patients) met criteria for past or present psychiatric disorder [10]. A subsequent study reported psychopathology in 51% of a larger cohort (68 of 133 patients) [11]. In both studies, identification

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of neuropsychiatric disturbance relied on Axis I diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorder (DSM)*. As such, mood symptoms that fell short of full diagnostic criteria were not counted among those CA patients with evidence of neuropsychiatric issues. Thus, the prevalence of CA-linked mood changes may be underestimated. While the Axis 1 diagnostic criteria indicate clinically relevant neuropsychiatric symptoms, sub-clinical mood state changes can also adversely impact symptom management, quality of life, and interpersonal relationships. Moreover, it is possible that CA may not manifest in a psychiatrically predictive manner (i.e., may not follow DSM criteria) given that localization of pathology is concentrated in the cerebellum. When studies evaluated symptoms using rating scales, which would allow detection of sub-clinical symptoms, typically only one class of symptoms was measured, such as depression, thereby overlooking the full spectrum of impairments [12–15]. Therefore, it is important to understand the nature and prevalence of neuropsychiatric changes associated with CA so that patients, caregivers, and clinicians can be prepared to address this class of symptoms as part of clinical care.

The current investigation aimed to characterize neuropsychiatric disturbance symptomology in CA, regardless of whether symptoms met full diagnostic criteria. We hypothesized that mood changes in CA are more prevalent than previously reported when accounting for sub-clinical symptomology. We were also interested in assessing information collected by patient informants (e.g., family and friends) whose insight and perspective may differ from the patient, helping to capture a full account of neuropsychiatric changes in patients. This was motivated by previous studies of non-motor symptomology in movement disorders (e.g., Parkinson's disease and Multiple Sclerosis) that found disagreement between patient and informant reports [16–18]. Likewise, the evaluation of perspectives of neuropsychiatric symptoms between patients and informants in this study could shed light on the impact of these symptoms in CA on close friends, family, and caregivers and guide patient education in the clinic.

Methods

CA Patients

Patients with CA ($N = 41$; females $= 23$; mean age $= 59.37$ years; age range $= 36$–82 years) were recruited from the Johns Hopkins Ataxia Center ($N = 36$) and the National Ataxia Foundation's Annual Ataxia Conference (San Antonio, 2017; $N = 5$). Inclusion criteria for this study were (1) diagnosis of progressive CA when other causes, including stroke, infection, head trauma, or environmental factors had been ruled out, and (2) an informant recommended by the

patient willing to participate in the study and knowledgeable about the patient's daily symptoms and changes with developing CA. Exclusion criteria for this study were (1) diagnosis with a major psychiatric condition under the DSM disorder that *predated* diagnosis of CA and (2) current or previous substance use dependence disorder.

CA diagnoses were verified by a trained movement disorders neurologist (LR) who categorized cases as either a known genetic subtype (e.g., a spinocerebellar ataxia [SCA] or autosomal recessive cerebellar ataxia type 1 [ARCA1]), familial ataxia, or cerebellar ataxia of unknown etiology (CAUE). These categorizations were based on information from personal and family health histories, clinical examination data, genetics, and neuroimaging. There were 17 patients with genetically confirmed CA subtypes: SCA1 ($N = 1$), SCA2 ($N = 1$), SCA3 ($N = 4$), SCA6 ($N = 8$), SCA8 ($N = 2$), and ARCA1 ($N = 1$). Familial ataxia ($N = 8$) was identified based on family history of CA in the absence of genetic subtype confirmation because testing was inconclusive or not performed. For purposes of this manuscript, we refer to the combined genetically confirmed and familial ataxia groups ($N = 25$) as *genetically acquired* ataxia. The remaining 16 patients were categorized as CAUE.

Scores from the Scale for the Assessment and Rating of Ataxia (SARA) and/or the International Cooperative Ataxia Rating Scale (ICARS) were available for 37 patients, and 14 received both assessments. The SARA ($N = 29$) and ICARS ($N = 22$) scores demonstrated that cases varied in severity from mild to moderate (Table 1). These scores corresponded with a mean disease duration since diagnosis of 7.95 years (SD $= 7.09$). A subset of patients ($N = 7$) were treated with antidepressants and/or psychotropic medications (e.g., fluoxetine, alprazolam, or diazepam) at the time of study participation, and no patients were undergoing counseling.

Table 1 Patient and healthy control demographics

	Patients ($N = 41$)	Controls ($N = 41$)
Age (mean, SD)	59.37, *11.26*	66.66, *7.02*
Education (mean, SD)	15.90, *2.67*	16.39, *2.63*
Gender (# of females, %)	23, *56.1*	23, *56.1*
Disease Duration (mean, SD)	7.95, *7.09*	–
ICARS Score (mean, SD)	33.64, *13.3*	–
SARA Score (mean, SD)	12.83, *4.46*	–
CES-D (mean, SD)	9.82, *9.0*	–

Disease duration = year of diagnosis from study enrollment. ICARS = International Cooperative Ataxia Rating Scale; SARA = Scale for the Assessment and Rating of Ataxia; CES-D = Center for Epidemiologic Studies Depression Scale

Healthy Controls

The CA neuropsychiatric state profiles were compared with healthy controls ($N = 41$; females $= 23$; mean age $= 66.66$ years; age range $= 48$–79 years). Control data were gathered from individuals with no neurological disorders who participated as controls in a study of Parkinson's disease (PD) and related disorders in the Morris K. Udall Parkinson's Disease Research Center of Excellence at Johns Hopkins University. Healthy control participants were retrospectively selected to match as closely as possible for sex, age, and education of the CA patient cohort. Although controls were well-matched to the CA group in terms of sex and education, the control cohort was older than the CA patients by approximately 7 years. However, Pearson correlations revealed no relation between age and number of reported neuropsychiatric symptoms within the control or patient groups.

CA Patient Informants

Each patient identified an informant who knew the patient prior to diagnosis with CA and regularly observed the patient's symptoms (CA informants: $N = 41$; mean age $= 57.5$ years old; age range $= 18$–81 years old; the age of one informant was missing from study records). The patient-informant relationship included spouse or partner of the patient ($N = 31$), adult child ($N = 4$), sibling ($N = 4$), or parent ($N = 2$). The inclusion of informant reports was intended to help identify the full range of patient symptoms, reveal the impact of CA on interpersonal relationships, and gauge patient insight into their own symptoms [19]. These goals for the inclusion of informants were supported by previous investigations of neuropsychiatric and cognitive changes in patients with movement disorders that found disagreement between patient and informant reports [16–18].

Informed consent was obtained from all participants prior to participating in this study. All study procedures were approved by the Institutional Review Board at Johns Hopkins University and performed in accordance with the Declaration of Helsinki.

Cerebellar Ataxia in-Person Interview

Psychiatric instruments designed for use in a broad spectrum of psychiatric disorders may not be suitable for people with CA. For example, "effortful" motor function may be rated as a symptom of depression, rather than of movement disorder on most depression scales. Moreover, subtle changes may be revealed more fully via conversational-style questions, rather than scripted statements that require yes and no responses or that limit focus on the recent past. To describe neuropsychiatric symptoms in CA patients, we asked open-ended questions about motor, cognitive, and emotion-related changes patients may have noticed in association with the onset of ataxia. Emotion and personality related changes were probed with questions such as, "To what extent do you feel impulsive, or act or speak without thinking first?" and "Have you noticed a change in your emotions since being diagnosed with cerebellar ataxia?". A mirrored interview was repeated with informants, allowing for direct comparison between patient and informant reports to identify convergent and divergent responses. Unlike standard clinical assessments and measures for neuropsychiatric disorders, these interviews allowed subclinical symptoms (i.e., below the formal threshold for standard psychiatric categories) to be captured and counted in the data analyses. The patient and informant interviews were administered by a trained researcher, with each interview lasting approximately 30–45 min.

Center for Epidemiologic Studies Depression Scale

Symptoms of depression were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) [20]. The CES-D is a 20-item, self-reported scale that measures states of depression within the previous 7 days from administration. CES-D scores were not collected for 3 patients recruited at the onset of this investigation. Informants and healthy controls were not administered the CES-D.

Evaluation of Neuropsychiatric Disturbance Symptomology

A framework for defining neuropsychiatric disturbance was necessary to distill and quantify the information acquired from the CA in-person interviews among standard categories of neuropsychiatric symptomology that were comparable with those reported in the literature. For this purpose, we selected the symptom domains of the Neuropsychiatric Inventory Questionnaire (NPI-Q), an abbreviated, cross-validated version of the Neuropsychiatric Inventory that is commonly used to evaluate neuropsychiatric disorders in neurodegenerative disease [21]. The NPI-Q evaluates 12 mood and psychiatric categories: delusions, hallucinations, agitation or aggression (referred to here as "agitation"), depression, anxiety, elation or euphoria (referred to here as "elation"), apathy or indifference (referred to here as "apathy"), disinhibition, irritability or lability (referred to here as "irritability"), motor disturbance (i.e., impulsive or perseverative behaviors, *not the motor deficits common in ataxia*), nighttime behaviors (e.g., insomnia or sleepwalking), and abnormal appetite [22]. NPI-Q scores reflect the presence or absence of symptoms within each of the 12 categories. If present, scores are also designated for symptom severity: mild, moderate, or severe.

Control NPI-Q scores were determined by self-report in a semi-structured interview administered by a trained research associate. Patient NPI-Q scores were derived from the CA

patient and informant in-person interviews and the patients' CES-D responses. Translation of the interview and CES-D information into NPI-Q scores was managed by consensus (SIK, CUO, CLM), led by a neuropsychiatrist (CUO) with expertise in neurodegenerative diseases, including CA and their neuropsychiatric complications. Each patient was initially given two NPI-Q ratings: one based on their own interview and CES-D and the second based on their informant report. Scores were provided for each of the 12 categories (present/absent) and severity. At the time of scoring, raters were blind to the other raters' assessments and the identity of the patient-informant pairs. After consensus rating of the independent patient and informant-based NPI-Q scores, the patient-informant pair NPI-Q scores were reconciled in a global score. Thus, each patient had three sets of NPI-Q scores available for assessment: patient-only, informant-only, and patient-informant reconciled global scores.

Statistics

Statistical analyses aimed to test (1) whether the frequency of positive NPI-Q symptoms among the CA patients differed from healthy controls and (2) CA patient subgroup NPI-Q symptom profile differences and (3) evaluate patient-informant pair symptom report disparities.

First, to test if the proportion of symptoms based on global NPI-Q scores within the patient sample was statistically *greater* than in healthy controls, ignoring symptoms severity, a one-tailed, binomial test was conducted for each symptom category, independently comparing the frequency of the NPI-Q category in the healthy control versus patient groups. Statistical analyses were not conducted for NPI-Q categories without patient and control occurrence (delusions, elation, and motor disturbance).

Next, analyses for prevalence of NPI-Q symptoms were conducted against subgroups of the CA patient cohort, which due to unique etiologies may offer insight into prevalence and origin of neuropsychiatric symptoms in CA. Prevalence among all NPI-Q categories determined by global scores were assessed with two-tailed, binomial tests between patients with genetically acquired ataxia ($N = 25$) versus CAUE patients ($N = 16$) and patients with SCA6 ($N = 8$) versus all other patients ($N = 33$) (Table 3). Subgroup comparisons are of interest because, while heterogeneity exists across all CA subgroups, the CAUE group potentially introduced further unknown etiological and pathological factors that could have skewed results due to unspecified non-cerebellar processes. Meanwhile, the neurodegeneration in SCA6 is relatively localized to the cerebellum; therefore, lower prevalence of symptoms within SCA6 group versus other patient types would indicate that extra-cerebellar pathology was a dominant driver of neuropsychiatric symptomatology [23].

Finally, the frequency of patient and informant pair NPI-Q symptom score disagreements was examined. One-tailed, binomial tests assessed if the frequency of patient-informant disagreements across NPI-Q symptoms was *greater* than the null hypothesis of no disagreements. For all NPI-Q categories that revealed a significant frequency of patient-informant disagreement, additional testing determined whether the patient or informant rated higher symptom severity. This was accomplished by finding among patient-informant pair disagreements in which cases the patient or informant reported higher symptom severity. Next, a two-tailed, binomial test determined if the proportion of either patients or informants reporting higher symptom severity significantly differed from the null proportion of 0.5, suggesting that among the disagreements within a particular NPI-Q symptom type, patients and their paired informant were equally likely to report higher symptom severity.

All analyses were implemented in MATLAB (www.mathworks.com) and IBM SPSS Statistics for Windows, Version 26 (IBM Corp., Armonk, N.Y., USA). For all determinations of statistical significance, p values were adjusted with Bonferroni correction for multiple comparisons.

Results

NPI-Q Symptoms—Patients Versus Healthy Controls

The global NPI-Q scores revealed that 39 of 41 (95.12%) CA patients presented with at least one NPI-Q symptom category. In fact, 30 patients (73.17%) scored with at least two symptoms and 21 patients (51.22%) were found with at least three symptoms (mean NPI-Q total score = 3.46, SD = 1.78). Symptoms were broadly represented among the NPI-Q categories (ranked by prevalence): anxiety (65.9%), depression (65.9%), nighttime behaviors (61.0%), irritability (56.1%), disinhibition (51.2%), abnormal appetite (22.0%), agitation (17.1%), apathy (4.9%), and hallucinations (2.4%) (Fig. 1; Table 2). No patients presented with a history of delusions, elation (e.g., mania), or motor disturbance, noting that the NPI-Q definition for motor disturbance is recurrent movements and not the common motor impairment profile in ataxia. Across patients and symptoms, severity was dominated by mild ($N = 103$) and moderate ($N = 36$) designations. Three patients were judged with the maximum symptom severity of severe for the irritability ($N = 2$) and depression ($N = 1$) symptom categories.

The proportion of patients within each of the NPI-Q categories was tested against the corresponding proportion in controls. One-way, binomial tests found the CA patients had greater symptom prevalence than did controls among the following NPI-Q categories: anxiety, depression, nighttime behaviors, irritability, disinhibition, abnormal appetite, and

Fig. 1 Global NPI-Q Scores and Distribution of Symptom Severity CA patient global NPI-Q scores of symptom severity represented by colored wedges: absent (blue), mild (yellow), moderate (orange), and severe (red). Asterisks indicate greater symptom prevalence in CA patients than in healthy controls by one-tailed, binomial statistical testing (see Table 2).
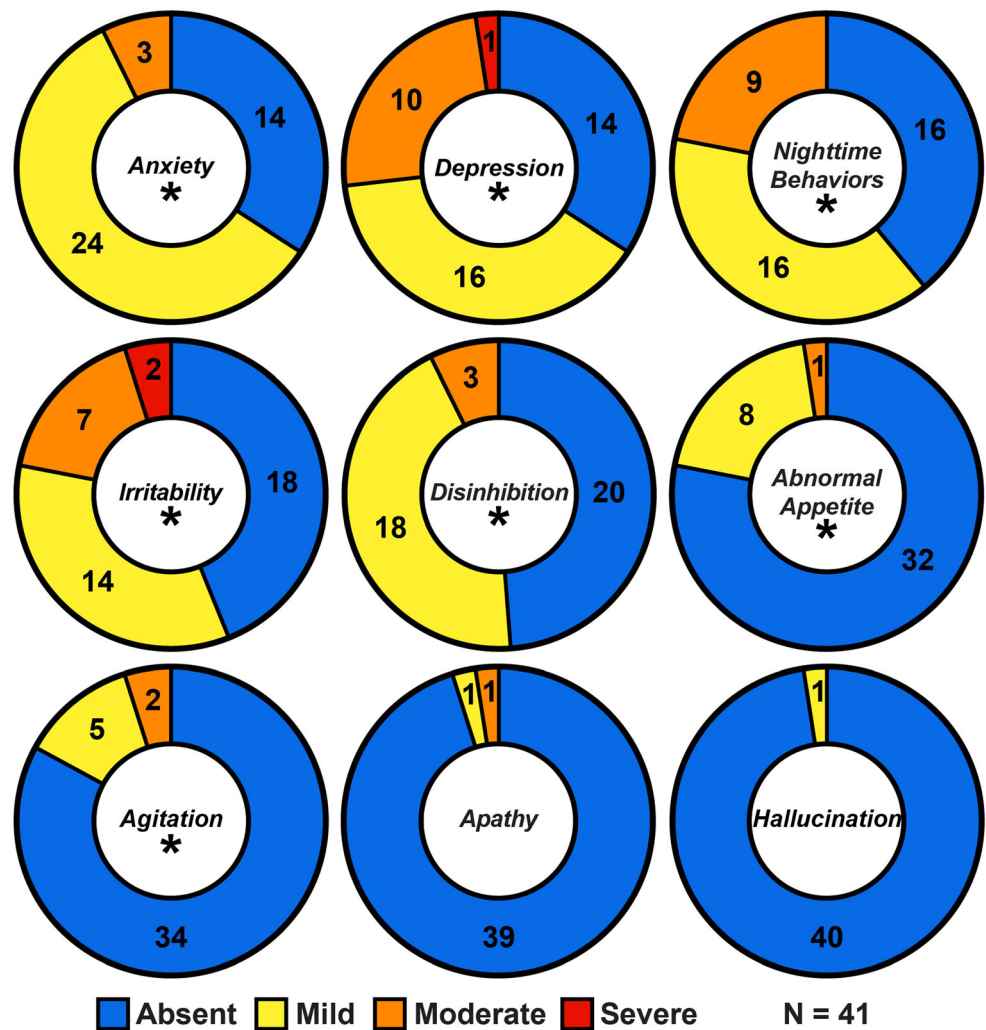

Table 2 NPI-Q Category Prevalence in Patients and Healthy Controls

NPI-Q Categories	Patients # (%) (N = 41)	Controls # (%) (N = 41)	P-values (one-tailed)
Anxiety	27 (65.9)	0 (0)	< 0.001*
Depression	27 (65.9)	6 (14.6)	< 0.001*
Nighttime Behaviors	25 (61.0)	13 (31.7)	< 0.001*
Irritability	23 (56.1)	3 (7.3)	< 0.001*
Disinhibition	21 (51.2)	0 (0)	< 0.001*
Abnormal Appetite	9 (22.0)	1 (2.4)	< 0.001*
Agitation	7 (17.1)	0 (0)	< 0.001*
Apathy	2 (4.9)	2 (4.9)	0.674
Hallucinations	1 (2.4)	0 (0)	0.040
Delusions	0 (0)	0 (0)	–
Elation	0 (0)	0 (0)	–
Motor Disturbance	0 (0)	0 (0)	–

NPI-Q category prevalence ranked by global reported frequency. P-values represent a one-tailed, binomial test of the proportion of NPI-Q symptoms in patient versus healthy controls (Bonferroni threshold = 0.006). Asterisks indicate a significantly greater symptom prevalence in patients than controls

agitation (all p values < 0.001). One patient presented with hallucinations, but this was not significantly different from the prevalence in controls at the Bonferroni corrected alpha threshold of 0.006 (0.05 divided by nine independent binomial tests for each NPI-Q category except for those without patient and control occurrence) (Table 2).

NPI-Q Symptoms—Patient Subgroup Comparisons

Patient subgroup NPI-Q prevalence by global score comparisons was completed between genetically acquired ataxia ($N = 25$) and CAUE patients ($N = 16$). Two-tailed, binomial tests revealed no significant difference of symptom proportion between subgroups (all p values > 0.10, except disinhibition and hallucination but neither survived the Bonferroni corrected alpha threshold of $p < 0.006$) (Table 3). Similar subgroup assessment using two-tailed, binomial tests compared the prevalence for each NPI-Q category by global scores between patients with SCA6 ($N = 8$) versus all other patients ($N = 33$). None of the tested NPI-Q categories reached significance (all

Table 3 NPI-Q Category Prevalence Distribution by Ataxia Etiology Subgroups

NPI-Q Categories	Genetically acquired # (%) (N = 25)	Unknown etiology # (%) (N = 16)	SCA6 # (%) (N = 8)	All Except SCA6 # (%) (N = 33)
Anxiety	17 (68.0)	10 (62.5)	4 (50.0)	23 (69.7)
Depression	17 (68.0)	10 (62.5)	6 (75.0)	21 (63.6)
Nighttime behaviors	15 (60.0)	10 (62.5)	4 (50.0)	21 (63.6)
Irritability	14 (56.0)	9 (56.3)	5 (62.5)	18 (54.5)
Disinhibition	15 (60.0)	6 (37.5)	6 (75.0)	15 (45.5)
Abnormal appetite	5 (20.0)	4 (25.0)	1 (12.5)	8 (24.2)
Agitation	3 (12.0)	4 (25.0)	1 (12.5)	6 (18.2)
Apathy	1 (4.0)	1 (6.25)	1 (12.5)	2 (6.1)
Hallucinations	1 (4.0)	0 (0)	1 (12.5)	0 (0)
Delusions	0 (0)	0 (0)	0 (0)	0 (0)
Elation	0 (0)	0 (0)	0 (0)	0 (0)
Motor disturbance	0 (0)	0 (0)	0 (0)	0 (0)

NPI-Q category prevalence divided by subgroups: genetically acquired versus unknown etiology and SCA6 versus all except SCA6. There were no subgroup differences determined by two-tailed, binomial statistical testing across NPI-Q symptoms following subgroup comparisons described in text (Bonferroni threshold = 0.006)

p values >0.10, except hallucination but above the Bonferroni corrected alpha threshold of $p < 0.006$). Taken together, these within-patient comparative analyses indicated that neuropsychiatric disturbances were consistent across all types of CA patients, thus a common phenomenology of CA, regardless of extra-cerebellar pathology.

NPI-Q Symptoms—Patient-Informant Agreement

There were 492 paired patient and informant NPI-Q symptom scores, representing 41 pairs each with 12 NPI-Q symptom categories. Patient-informant pair disagreements were determined when the corresponding patient and informant NPI-Q symptom scores did not match (e.g., a patient indicated a present symptom while the informant reported that symptom absent, or an informant reported greater symptom severity than the corresponding paired patient). There were 115 patient-informant pair disagreements (23.37% of total number of scores), spanning across all patients and symptoms, except delusions, elation, and motor disturbance where no symptoms were reported (Fig. 2). The average total number of patient-informant score disagreements across symptoms was 2.81 disagreements per pair (SD = 1.54; range = 0–6), indicating that disagreements were common and widely distributed among patient-informant pairs, not dominated by a subset of pairs. Also, of the 115 disagreements, there was a near-even split for instances where patients (N = 57) or informants (N = 58) reported higher symptom severity, suggesting that when collapsed across NPI-Q categories there was no bias for patients or informants to report more severe symptoms.

One-tailed, binominal tests against the null proportion of no disagreements revealed a statistically significant proportion
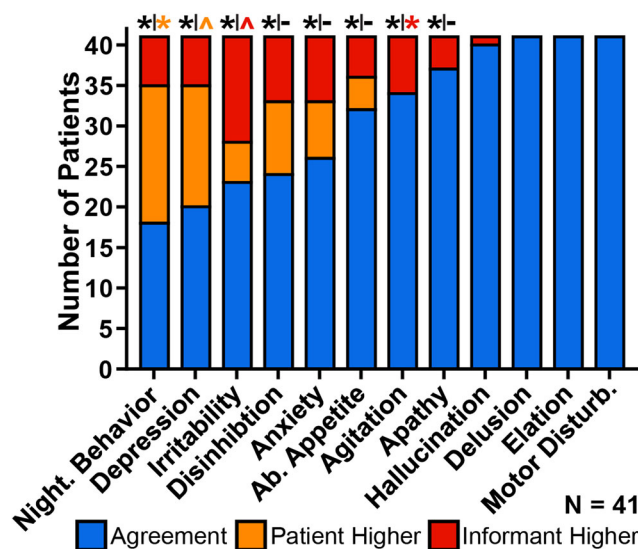

Fig. 2 Patient versus Informant NPI-Q Score Agreement and Disagreement. Agreement and disagreement scores on the NPI-Q were compared between CA patients and informants. Bar colors indicate the categories of patient-informant pair reporting: blue = no group disagreement; orange = higher symptom severity scoring by patients; red = higher symptom severity scoring by informants. Symbols above each NPI-Q symptom bar indicates whether the patient-informant pair disagreements were significantly above the null hypothesis of no disagreements (left asterisk) and whether that statistically significant level of disagreement was driven by either the patients or informants reporting more severe symptoms (right asterisk), indicated by the asterisk color: orange = patient-driven disagreements; red = informant-driven disagreements. */* = significant disagreements and group bias; */^ = significant disagreements and trending group bias; */– = significant disagreements and no group bias

of patient-informant disagreements for nighttime behaviors, depression, irritability, disinhibition, anxiety, abnormal appetite, agitation, and apathy (all Bonferroni adjusted p values < 0.001; Fig. 2). Post-hoc, two-tailed, binominal tests determined that relative to informants, patients were more likely to report higher symptom severity scores for nighttime behaviors (p value < 0.05) and depression (marginal p value < 0.10) (Fig. 2). By contrast, relative to patients, informants were more likely to report higher symptom severity scores for agitation (p value < 0.05) and irritation (marginal p value < 0.10).

Discussion

This study found a high prevalence of neuropsychiatric symptomology in patients with CA. Previous studies reported a history of neuropsychiatric disorders in CA at a rate of between 51 and 77% [10, 11]. Expanding on these findings, we found that nearly all patients (39 of 41 patients; 95.12%) exhibited symptoms of neuropsychiatric disturbance when sub-clinical diagnostic criteria were considered. Previous studies have used standardized measures of psychiatric symptoms to examine symptomology in CA. These measures have the advantage of being validated in psychiatric syndromes and widely used. However, they are designed to measure major psychiatric syndromes and may be too conservative to capture sub-clinical phenomena. Correspondingly, the approach implemented in this investigation of a semi-structured interview specifically designed for CA to gather details about non-motor symptoms may be more sensitive. Indeed, when symptoms do not reach standard thresholds for the major psychiatric syndromes, they can still have major impacts on quality of life of patients and families [24–27].

The current results showed that neuropsychiatric symptoms in CA clustered among a subset of categories: anxiety, depression, disinhibition, irritability, sleep disturbance, and agitation. Previous studies agree with reports of depression and anxiety in CA [11, 12]. While the other frequent symptom types reported in the current investigation, including disinhibition, irritability, and agitation, are less commonly described in CA, there are links to these specific affect regulation impairments and cerebellar damage [28–33].

In prior studies, psychosis (hallucinations and delusions) has been observed in 10% of CA patients [10, 11, 34]. In contrast, we only observed hallucinations in one patient and no cases of delusions or mania. This discrepancy may be explained by differences in sampling strategy and exclusion of patients with psychiatric diagnoses that predated their CA. It is also possible that the distribution of CA subtypes differed across studies, resulting in divergent neuropsychiatric profiles. Regardless, our findings agree with the literature that mood disturbances are more commonly associated with CA than are psychotic episodes.

The methodological constraints and results of the current study highlight a need for assessments of neuropsychiatric symptomology sensitive for people with cerebellar degenerative disease. A neuropsychiatric profile included in the Cerebellar Cognitive Affective Syndrome (CCAS) contains five major domains: emotional control, social skills, autism spectrum, psychosis spectrum, and attentional control [35, 36]. These domains were derived from heterogeneous samples of patients (children and adults) with various types of cerebellar injury, including cerebellar tumor, stroke, virus, and degeneration. While the current study was limited to patients with progressive cerebellar degenerative disease, we observed overlap with some of the five CCAS domains. The largest overlap was found within the domain of emotional control, which included agitation, anxiety, depression, disinhibition, and lability [36]. Aggression and irritability that comprise a portion of the social skills domain were also observed in the current cohort. However, we did not find symptoms within the autism or psychosis spectrums. Unlike the CCAS, the NPI-Q did not assess attention directly. However, the NPI-Q assessed nighttime behaviors and appetite, both of which were more prevalent in the cerebellar patients than in controls and neither are included among the CCAS domains. Therefore, the CCAS domains did not fully apply to this cohort of patients with cerebellar degeneration. Rather, these data suggest that CA patients may present a specific set of neuropsychiatric manifestations that differ from patients with other types of cerebellar injuries. That current standardized neuropsychiatric assessment may not adequately detect impairments in cerebellar patients has been noted previously [35] and underscores the need for further test refinement.

The cerebellum is the major site of pathology in CA patients; however, debate continues on the role of extra-cerebellar influences for driving the neuropsychiatric changes reported in CA. Without neuroimaging, the extent of disease outside the cerebellar cannot be determined among the patients recruited for the current investigation. However, we confirmed that when the influence of extra-cerebellar brain regions was minimized in our analyses, such as an analysis of the SCA6 group separately known for more focal cerebellar degeneration, a high prevalence of neuropsychiatric symptoms remained. Moreover, the prevalence of symptoms in the SCA6 group did not differ from the other patients with divergent CA diagnoses. This suggests that neuropsychiatric disturbance in patients with CA is a reliable phenomenon that accompanies the disorder, regardless of etiology. Future studies should include non-cerebellar control groups to determine whether the neuropsychiatric profile identified in this and other studies is unique to cerebellar patients or overlaps with behavioral changes encountered in other movement disorders associated with neurodegeneration.

A novel aspect of the current study was evaluation of patient versus informant perspectives on neuropsychiatric symptoms associated with CA. We found that patient-informant pair disagreements were common. Patients reported higher severity of sleep impairment and depression than did their informants. By contrast, the informants emphasized symptoms of irritability and agitation. In some cases, these may represent different perspectives on the same symptoms. For example, what a patient may experience as anxiety could be perceived by the informant as agitation, or the patient's outward expression of that anxiety. Likewise, the experience of depression and sleep disturbance may be very salient to the patient, whereas the informant may be more sensitive to irritability that is present in interpersonal interactions. Alternatively, patients may lack insight into their own symptoms. Regardless, patient-informant disagreement implies that clinical evaluations would benefit from family input to fully comprehend the neuropsychiatric status of CA patients. Moreover, such input would help characterize the full impact of symptoms on the quality of life for the patient and family.

Limitations

Identifying the neural mechanisms of mood changes and affect regulation in CA is of primary clinical interest to guide treatment approaches. It is challenging to attribute neuropsychiatric disturbance in CA solely to the cerebellum because, while CA patients share varying degrees of degeneration of the cerebellum, the neuropathology can extend beyond the cerebellum [1, 37]. Indeed, a primary limitation of the current investigation in this regard is the heterogeneity of the CA patients, some of whom may have extra-cerebellar brain regions affected. Although the role of the cerebellum in mood and psychiatric symptoms has been acknowledged, the precise mechanism of the cerebellum in emotion or affect regulation are unknown [9, 31, 32, 38, 39]. Cerebellar connections to the limbic network, including the cingulate cortex, amygdala, and ventral tegmental area suggest a role in the regulation of affective state [40–42]. This corresponds with neuroimaging findings that implicate the cerebellum in managing emotional state [10, 31, 35, 43–45]. Future investigations should aim to clarify the mechanism by which the cerebellum contributes to emotional states and relate this to the symptom profiles in patients with cerebellar damage.

A second limitation of this study is the exclusion of patients with a history of neuropsychiatric illness that predated the onset of CA. This exclusion provided a conservative accounting of symptoms that were most likely related to CA. Notably, Leroi and colleagues (2002) found neuropsychiatric disturbance present before the onset of motor symptoms in only 1 of 31 CA patients. It is possible, however, that prodromal mood symptoms are part of the CA course, similar to Huntington's disease [46]. To fully account for prodromal

symptoms in CA would require longitudinally following at-risk patients, prior to motor symptom onset.

Third, the heterogeneous methodology used to obtain patient and control NPI-Q scores, by consensus rating and self-report, respectively, possibly confounded the direct comparisons between groups. The NPI-Q was chosen as a framework for categorizing and designating the severity of symptoms reported in the CA interviews. The consensus rating was implemented as a rigorous method of arriving at these determinations across patient-informant pairs. Although differences between patient and control NPI-Q scores may partially be explained by the divergent methods used to arrive at these scores, the large contrast between patient and control symptomology reports suggests that between-group variance is unlikely to be fully explained by differences in scoring methods.

Conclusion

Changes in mood states are common in CA, affecting 95% of the current cohort and representing a reliable phenomenology of the disease. This high rate of neuropsychiatric dysregulation underscores the need for clinicians to probe for and monitor signs of neuropsychiatric dysfunction in CA patients. Moreover, our findings demonstrate that informants can provide useful collateral information regarding neuropsychiatric status and thereby better inform clinicians of non-motor symptoms. Increased awareness of symptoms linked to mood changes could improve clinical treatment and quality of life for CA patients and their families.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Approval All study procedures were approved by the Institutional Review Board at Johns Hopkins University and performed in accordance with the Declaration of Helsinki.

Consent to Participate Informed consent was obtained from all participants prior to participating in this study.

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