

Neurologic Manifestations of Common Variable Immunodeficiency

Impact on Quality of Life

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Abstract

Background and Objectives

Common variable immunodeficiency is a systemic disease and not solely a disease of humoral immunity. Neurologic symptoms associated with common variable immunodeficiency are underrecognized and warrant further study. This work aimed to characterize the neurologic symptoms reported by people living with common variable immunodeficiency.

Methods

We conducted a single academic medical center study of neurologic symptoms reported by adults previously diagnosed with common variable immunodeficiency. We used a survey of common neurologic symptoms to determine the prevalence of these symptoms in a population with common variable immunodeficiency and further assessed these patient-reported symptoms with validated questionnaires and compared symptom burden with other neurologic conditions.

Results

A volunteer sample of adults (aged 18 years or older) previously diagnosed with common variable immunodeficiency at the University of Utah Clinical Immunology/Immune Deficiency Clinic who were able to read and comprehend English and willing and able to answer survey-based questions were recruited. Of 148 eligible participants identified, 80 responded and 78 completed the surveys. The mean age of respondents was 51.3 years (range 20–78 years); 73.1% female and 94.8% White. Patients with common variable immunodeficiency reported many common neurologic symptoms (mean 14.6, SD 5.9, range 1–25), with sleep issues, fatigue, and headache reported by more than 85%. Validated questionnaires addressing specific neurologic symptoms supported these results. T-scores on Neuro QoL questionnaires for sleep (mean 56.4, SD 10.4) and fatigue (mean 54.1, SD 11) were higher, indicating more dysfunction, than in the reference clinical population ($p < 0.005$). The Neuro QoL questionnaire for cognitive function showed a lower T-score (mean 44.8, SD 11.1) than that in the reference general population ($p < 0.005$), indicating worse function in this domain.

Discussion

Among survey respondents, there is a marked burden of neurologic symptoms. Given the impact of neurologic symptoms on health-related quality-of-life measures, clinicians should screen patients with common variable immunodeficiency for the presence of these symptoms and offer referral to neurologists and/or symptomatic treatment when indicated. Frequently prescribed neurologic medications may also affect the immune system, and neurologists should consider screening patients for immune deficiency before prescribing them.

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Glossary

CVID = common variable immunodeficiency; **HRQL** = health-related quality of life; **ICD** = *International Classification of Diseases*; **MIDAS** = Migraine Disability Assessment; **OABSS** = Overactive Bladder Symptom Score; **USIDNET** = United States Immunodeficiency Network.

Common variable immunodeficiency (CVID) is the most common primary immunodeficiency of adults with an estimated prevalence between 1:10,000 and 1:100,000 worldwide and approximately 1:67,000 in the United States.¹⁻³ CVID is characterized by low immunoglobulin levels with low or absent antibody production, resulting in recurrent infections and poor or no response to vaccinations.² Despite the common presenting immunologic defect of hypogammaglobulinemia, the pathways that lead to this defect in patients with CVID are varied. Between 10% and 20% of cases with CVID have been shown to have a heritable cause to date; monogenic forms of CVID account for 2%–10% of patients, and the remainder of cases are polygenic or multifactorial.⁴ Clinical phenotypes in patients with CVID are highly variable, ranging from no complications to multisystem autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancy.⁵ Neurologic manifestations of CVID have historically largely been attributed to complications from infections of the nervous system or secondary to autoimmune/inflammatory causes.⁶ To date, limited epidemiologic data on the co-occurrence of CVID and neurologic disorders and/or related symptoms has been reported. Using surveys of patient-reported neurologic symptoms, we sought to characterize the prevalence of these symptoms in our immunodeficiency clinic population.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Protocols and procedures of this study were approved by the Institutional Review Board of the University of Utah. Participation was voluntary, and written informed consent was obtained from all study participants or their surrogates before distribution of the surveys.

Study Design

We conducted a questionnaire-based, prospective, epidemiologic study designed to establish the presence and prevalence of reported neurologic symptoms in adults diagnosed with CVID at the University of Utah. Patients were initially identified using a retrospective chart review from July 1, 2010, to September 21, 2017, within the University of Utah School of Medicine electronic medical record system and including at least 1 ICD-9 (279.*) or ICD-10 codes (D80.*, or D83.*) consistent with CVID. Inclusion criteria for this survey study were age 18 years or older, previous diagnosis of CVID at the University of Utah Clinical Immunology/Immune Deficiency Clinic by European Society of Immunodeficiencies and Pan-American Group for

Immunodeficiency criteria, ability to read and comprehend English, and willingness to answer survey-based questions.^{7,8} Patients younger than 18 years, unable to read and comprehend English, not meeting diagnostic criteria for CVID, or unwilling to answer the survey-based questions were excluded from this study.

Assessment Tools

Patient demographic information including age, sex, and race/ethnicity was self-reported on the initial screening form. The questionnaire-based assessment consisted of 2 types of surveys: a nonvalidated questionnaire and validated questionnaires. After an exhaustive literature search, we were not able to identify any validated self-assessment instruments that would identify the highest incident and/or most prevalent neurologic symptoms in patients with CVID. Therefore, a group of 5 neurologists and 2 neuroscientists at the University of Utah created a 25-question neurologic symptom self-assessment questionnaire (Q1) based on the most prevalent neurologic symptoms reported in their general and subspecialty neurology clinics. The questions were designed to be as simple as possible, containing only questions about neurologic symptoms encountered at a typical medical visit, and formulated to be understood by an individual with an 8th grade education. Participants were either e-mailed a link through which they were able to answer the questions or mailed a paper copy of the questionnaires to their homes. This screening questionnaire asked patients to indicate “How long have you experienced the following neurologic problems?”; the problems asked about are detailed in the Table. After consenting and answering the Q1 screening questionnaire, patients next completed validated symptom-specific questionnaires: Overactive Bladder Symptom Score (OABSS), Indiana Polyclinic Combined Pain Scale, Migraine Disability Assessment (MIDAS), and Neuro-QoL Short Forms assessing fatigue (v1.0), depression (v1.0), cognitive function (v2.0), and sleep disturbance (v1.0)—available for review at healthmeasures.net.⁹⁻¹² The OABSS questionnaire consists of 4 symptoms (daytime frequency, nighttime frequency, urgency, and urgency incontinence) and a scoring system for the frequency of these symptoms.¹¹ The Indiana Polyclinic Combined Pain Scale consists of a numerical rating (from 0 to 10) and a verbal description of pain intensity (from no pain rated at 0 to worst imaginable pain rated at 10) and the impact it has on the ability to function on a daily basis (from no interference with activity rated at 0 to totally dependent due to pain rated at 10). For example, a pain intensity score of 3 corresponds to mild pain (tolerable, but unsettling and on one’s mind. Interferes with pleasures of life. Stops some productive activities. Examples: scraped knee, jammed finger), and a pain intensity score of 4 corresponds to mild-to-moderate pain (only short intervals of

Table Patient-Reported Neurologic Symptoms

	Number reporting symptom/number responding (%)
Sleep problems: difficulty falling asleep, staying asleep, waking up, and sleeping more than usual	68/78 (87.2)
Fatigue	67/78 (85.9)
Headache	66/77 (85.7)
Changes in muscles: cramps and twitching	61/77 (79.2)
Pain of unclear cause	56/73 (76.7)
Numbness, tingling, tightness, or burning	59/77 (76.6)
Changes in vision: blurred vision, difficulty focusing	58/78 (74.4)
Difficulty concentrating or focusing	57/76 (75)
Memory difficulty: problems remembering	57/78 (73.1)
Muscle weakness	54/77 (70.1)
Vertigo or dizziness	52/77 (67.5)
Depression	50/78 (64.1)
Changes in hearing	48/76 (63.2)
Syncope or feeling like you are going to pass out	44/77 (57.1)
Bowel incontinence/constipation	44/78 (56.4)
Olfaction abnormalities	42/76 (55.3)
Balance changes or falls	38/76 (50)
Difficulties with coordination or walking	39/78 (50)
Urinary incontinence; retention	34/77 (44.2)
Changes in taste: things tasting differently than they used to, tasting better, tasting worse	32/77 (41.6)
Changes in speech	26/77 (33.8)
Dystonia: uncontrolled muscle movements	25/77 (32.5)
Seeing double images	25/78 (32.1)
Difficulty swallowing	24/77 (31.2)
Seizures or epilepsy	10/78 (12.8)

comfortable function, sometimes interrupts activities of daily living, such as bathing and clothing, and regularly prevents involvement in many tasks outside of the home. Decrease in job performance. Examples: major bruise, ankle sprain). A pain impact score of 2 would correspond to the following: can work/volunteer a few hours daily; active 5 + hr/d; can plan and keep 1–2 social events during evenings/weekends; can complete household/yard work with some strain, may need help with select activities. The MIDAS questionnaire consists of 5 questions about disability associated with headache experienced in the preceding 3 months; a MIDAS score of 0–5 indicates little or no disability (MIDAS grade I), a score of 6–10 indicates mild disability (MIDAS grade II), 11–20 moderate disability (MIDAS grade III), and 21 + severe disability (MIDAS grade IV)

due to headache.^{12,13} Neuro-QoL short-form questionnaires consist of 8 symptom questions that ask whether symptoms in that domain have been experienced “In the past 7 days...,” scored as 1 (never), 2 (rarely), 3 (sometimes), 4 (often), or 5 (always); raw scores range from 8 to 40.

Data Analysis and Statistical Method

REDCap was used to procure and store data. Participant’s demographics and characteristics were obtained through REDCap, and analysis was performed in Stata 16.1 (Stata-Corp, College Station, TX). Neuro-QoL short-form questionnaire scores were converted to standardized T-scores using the Neuro-QoL Health Measures Scoring Service (assessmentcenter.net/ac_scoring-service). T-scores provide a standardized score in which the mean of a relevant reference population is 50 and 10 is the SD of that reference population. The reference population used was either the US general population (depression and cognitive function) or a clinical population (fatigue and sleep disturbance).⁹ The reference clinical population used to develop the Neuro-QoL consisted of patients with stroke, epilepsy, multiple sclerosis, Parkinson disease, and amyotrophic lateral sclerosis. Higher T-scores indicate more of the construct being measured; for negatively worded concepts such as fatigue, a higher T-score represents greater fatigue. For positively worded concepts such as cognitive function, a higher T-score represents better cognitive performance. For OABSS, MIDAS, and Indiana Polyclinic Combined Pain scale sections, raw scores were used to calculate a mean and SD for normally distributed data (using the Shapiro-Wilk test of normality) or median and interquartile range (IQR) for non-normally distributed data (see eFigure 1, links.lww.com/NXI/A803 for histograms showing data distribution). For NeuroQoL surveys, comparisons between patients with CVID and other neurologic diseases or the reference population were performed by the Student *t* test and adjusted for multiple comparisons using Finner multiple comparison procedure. Similar to the Bonferroni procedure, the Finner¹⁴ procedure maintains the desired alpha (0.05) regardless of the correlation structure of the endpoints, while being more powerful than the Bonferroni procedure.

Data Availability

Reasonable requests from any qualified investigator for anonymized data will be satisfied.

Results

Study Participants

A total of 178 patients was identified at our institution with confirmed CVID for this study. Of them, 8 were deceased, 1 was underage, and 21 had incorrect contact information and were therefore excluded. We reached out to 148 eligible participants; 80 responded to the survey (54.1% response rate). Of those who responded, 78 (97.5%) completed the survey. These respondents had a mean age of 51.3 years (range 20–78); 57 (73.1%) respondents were identified as

female; 74 (94.8%) respondents were White, 2 (2.6%) were Hispanic/Latino, and 2 (2.6%) identified their race/ethnicity as “other.”

Patient-Reported Symptoms

The presence of common neurologic symptoms was determined using the 25-item Q1 survey we created, with responses categorized as “ever” or “never” regardless of the duration reported (Table). Of note, not all survey respondents answered every question on the survey, as summarized in the Table. Of importance, this questionnaire was intentionally broad so as to allow us to capture as many symptoms in this screening study as possible, which can help guide future research to focus on more specific areas of interest. Most patients reported many symptoms, with the mean number of reported symptoms 14.6 (SD 5.9, range 1–25). The most frequently reported symptoms were sleep problems (87.2%), fatigue (85.9%), headache (85.7%), fasciculations (79.2%), pain (76.7%), paresthesia (76.6%), memory issues (73.1%), and concentration issues (73.1%). Notably, sleep issues, fatigue, and headache were each reported by more than 80% of study participants. The neurologic symptoms for which validated patient surveys were available during our study were further explored; regardless of the answers to the screening questionnaire, participants were included in the validated surveys.

Sleep Problems

Sleep problems (difficulty falling asleep, staying asleep, waking up, and sleeping more than usual) were the most common neurologic symptoms reported in our CVID population, with 87.2% of survey respondents indicating sleep difficulties. Using the Neuro QoL Sleep Disturbance Short Form Questionnaire, we further evaluated the extent of sleep disturbance on patient quality of life. A T-score more than 50 indicates more sleep disturbance (difficulty falling asleep, staying asleep, and daytime sleepiness) than the reference clinical population. The reference clinical population used to develop the Sleep Disturbance Neuro-QoL consisted of patients with neurologic disease—stroke, epilepsy, multiple sclerosis, Parkinson disease, and amyotrophic lateral sclerosis. Of the 76 patients who completed this questionnaire, the mean T-score was 56.4 (range 32–77.3, SD 10.4). This score indicates higher levels of sleep disturbance in our CVID population than in the reference clinical population and in prior studies of patients with multiple sclerosis, Parkinson disease, epilepsy, and stroke ($p < 0.05$, Figure 1A).

Fatigue

Fatigue was the second most frequently reported neurologic symptom among survey respondents, with 85.9% of our patients reporting fatigue. The Neuro QoL Fatigue Short-Form Questionnaire was used to further evaluate this symptom in our patients. A T-score more than 50 indicates more fatigue than the reference clinical population. The reference clinical population used to develop the Fatigue Neuro-QoL consisted of patients with neurologic disease. Of the 76 patients who

completed this questionnaire, the mean T-score was 54.1 (range 29.5–74.1, SD 11), indicating levels of fatigue in patients with CVID, which were significantly worse than those in the reference clinical population and in other studies of patients with multiple sclerosis, Parkinson disease, stroke, and epilepsy ($p < 0.05$, Figure 1B).

Headache

A history of headache was reported by 85.7% of our survey respondents. We used the MIDAS self-assessment questionnaire to better understand the impact of headaches in our CVID population. Of the 73 people who completed this questionnaire, the mean MIDAS score was 15.5 (range 0–125, SD 25). Given the large SD and skewed distribution in these data (eFigure 1, links.lww.com/NXI/A803), the median of 2 (IQR 0–25) better represents the impact of headache in our survey respondents. While 58.9% of survey respondents reported little to no disability from their headaches (MIDAS grade I), the remaining 41.1% were MIDAS grade II or higher, with 28.8% reporting MIDAS grade IV, indicating severe disability from their headaches.

Pain

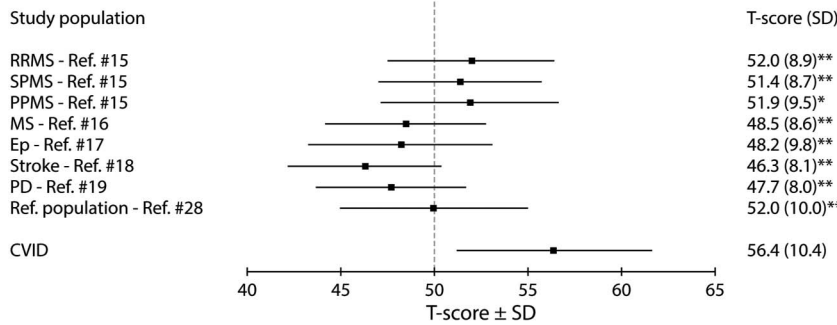
Pain of unclear cause was reported by 76.7% of our survey respondents. To better understand pain in our CVID population, we used the Indiana Polyclinic Combined Pain Scale. This scale consists of a numerical rating (from 0 to 10) and a verbal description of pain intensity (from no pain rated at 0 to worst imaginable pain rated at 10) and the impact it has on the ability to function on a daily basis (from no interference with activity rated at 0 to totally dependent due to pain rated at 10). We had 75 survey respondents who completed this 2-item scale. The mean pain intensity was 3.4 (range 0–8, SD 2). This pain level corresponds to between mild pain and mild-to-moderate pain. The median impact on overall daily function due to pain was 2 (range 0–8, IQR 1–4). This impact score corresponds to minimal limitations. These scores suggest that while not severe, pain affects most people with CVID because only 12% of survey respondents reported no pain and only 21.3% reported no interference with activity.

Cognitive Function

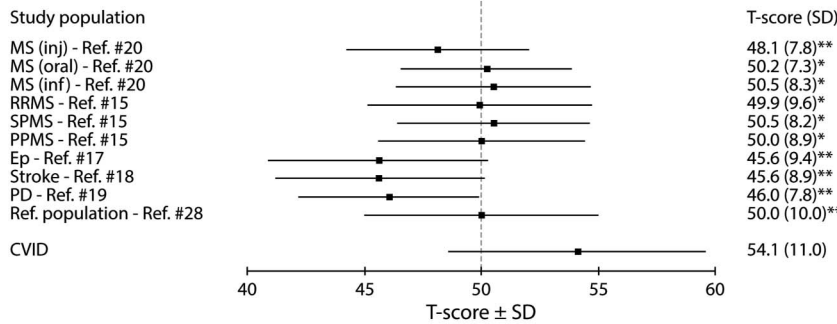
Cognitive symptoms were frequently reported in our CVID population, with 75% reporting difficulty concentrating/focusing and 73.1% reporting memory difficulty. The Neuro QoL Cognitive Function Short-Form Questionnaire was used to better assess subjective cognitive difficulties in our population. A T-score of 50 represents cognitive performance at the level of the US general population, with a score greater than 50 indicating better cognitive function and a score less than 50 indicating worse cognitive function. The mean T-score of the 76 survey respondents who completed the Cognitive Function Neuro QoL was 44.8 (range 25.7–64.2, SD 11.1). This is similar to the amount of cognitive dysfunction reported in several prior studies of people with primary neurologic diagnoses, including multiple sclerosis, early-stage Huntington disease, and a history of traumatic brain injury. It is worse than

Figure 1 Neuro QoL Results for Patients With CVID and Other Published Neurologic Diseases¹⁵⁻²³

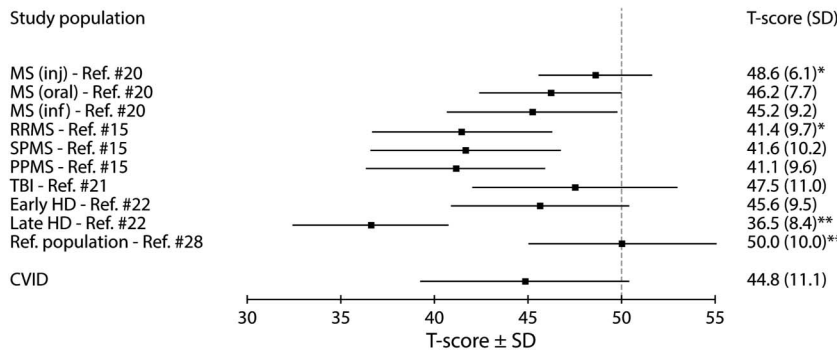
A. Sleep disturbance



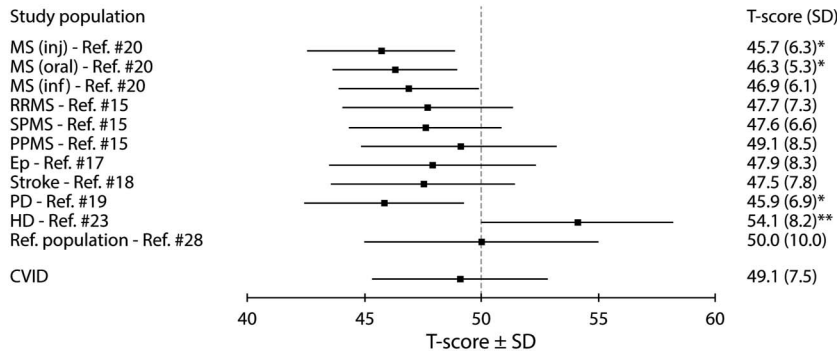
B. Fatigue



C. Cognitive function



D. Depression



Neuro QoL T-scores from our patients with CVID for sleep (A), fatigue (B), cognitive function (C), and depression (D) plotted with published data of patients with other neurologic diseases. * $p < 0.05$, ** $p < 0.005$ adjusted using Finner multiple comparison procedure. Ep = epilepsy; HD = Huntington disease; MS = multiple sclerosis; PD = Parkinson disease; PPMS = primary progressive multiple sclerosis; Ref Pop = reference population; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; TBI = traumatic brain injury.

that reported by the reference population ($p < 0.005$). Not surprisingly, patients with late-stage Huntington disease performed worse than our CVID population in this domain ($p < 0.005$, Figure 1C).

Depression

Depression was a commonly reported symptom in our screening questionnaire, with 64.1% of our CVID population reporting ever having depression. We used the Neuro QoL

Depression Short-Form to further assess depression in our participants. Of the 76 survey respondents, the mean T-score was 49.1 (range 36.9–68.4, SD 7.5), which is similar to the US reference general population T-score for depression of 50 with an SD of 10. This is also similar to the depression scores seen in primary neurologic disease, including multiple sclerosis, stroke, epilepsy, and Parkinson disease; it is lower than has been reported for patients with Huntington disease ($p < 0.005$, Figure 1D).

Urinary Incontinence/Retention

Urinary symptoms (either incontinence or retention) were reported by 44.2% of our survey respondents. To better understand the urinary symptoms of our patients with CVID, we administered the OABSS questionnaire. This questionnaire consists of 4 symptoms (daytime frequency, nighttime frequency, urgency, and urgency incontinence) and a scoring system for the frequency of these symptoms. There were 77 patients with CVID who completed the OABSS questionnaire, with a median score of 3 (range 0–9, IQR 2–6).

Discussion

Our survey results demonstrate that people living with CVID experience many common neurologic symptoms, often at a rate comparable with primary neurologic conditions.^{15–28} The average patient reported more than 14 of the 25 common neurologic symptoms included in our screening survey. There is a dearth of published data regarding neurologic symptoms in people living with CVID. One published thorough literature review of neurologic disease associated with CVID found that reports focused largely on symptoms due to infectious, autoimmune, or inflammatory processes, with a few cases related to endocrine or nutrient deficiency,²⁹ while another study utilized the United States Immunodeficiency Network (USIDNET) physician-reported patient registry to characterize neurologic conditions and symptoms in records of patients with CVID and found that 42.1% recorded at least 1 neurologic condition or symptom.³⁰ While the USIDNET paper used registry data and ours used patient-reported surveys, both highlight that neurologic complications are more common in CVID than previously recognized. It is important to remember that CVID is not simply a disease of humoral immunity; autoimmune and inflammatory responses from dysregulated immunity can affect all organ systems, including the nervous system, resulting in non-specific symptoms such as those reported in this study. Many symptoms reported by our patients are known to co-occur, such as sleep disturbance, fatigue, and depression.^{31,32} While this study was not designed to disambiguate the impact that each of these symptoms may have on one another, clinical evaluation of patients reporting these symptoms should keep this overlap in mind.

Many people diagnosed with CVID experience a significant delay in diagnosis of between 5 and 10 years³³ When a diagnosis is obtained, often in a subspecialty immunology clinic,

the focus of management is largely on preventing and treating infection(s) and secondarily on vigilance diagnosing associated autoimmune diseases, lymphoproliferative disorders, malignancy screening, and gastrointestinal complications.³⁴ Other studies have shown that delayed diagnosis was correlated with some health-related quality of life (HRQL) dimensions in pediatric and adult patients, suggesting that early diagnosis and treatment may improve some of these HRQL parameters.^{35,36} Because our study relied on patient report rather than collection of data from clinical charts, we were unable to confirm any possible relationship between delay in diagnosis and HRQL. Given the long diagnostic delay patients often experience, they may have been subjected to treatment for other conditions, which can confound immunodiagnostic studies when they do see immunologists. Medications such as corticosteroids, mycophenolate mofetil, rituximab, ocrelizumab, and anticonvulsants have been linked to low immunoglobulin levels, and some may suppress responses to vaccination.^{37–39} Before initiating treatment with such medications, screening for signs of immunodeficiency in these patients should be considered. More research on the effects of medications on immunologic responses is needed going forward.

Our study suggests that there is likely an underrecognition of neurologic symptoms and complications that have a significant impact on HRQL. The increased recognition of the importance of HRQL in neurologic conditions prompted the National Institute of Neurologic Disorders and Stroke to develop clinically relevant measures of social, mental, and physical well-being in patients with neurologic disorders.³⁴ We were able to use these tools to further explore the HRQL in our CVID population, specifically for sleep problems, fatigue, cognitive function and depression. While a powerful tool, these surveys address only a small subset of the symptoms commonly reported by patients seen in our neurology clinics. We found that sleep problems and fatigue in our CVID population were more marked than in patients with other neurologic disorders, such as multiple sclerosis, epilepsy, stroke, and Parkinson disease. Cognitive function was worse than the general reference population and similar to what is reported in primary neurologic diseases with *known* cognitive impairment, such as multiple sclerosis and brain injury. Overall, these findings underscore the importance of recognizing and evaluating for the presence of neurologic manifestations of CVID and referring patients to neurologists for further evaluation and treatment. A related challenge in the assessment of neurologic symptoms in clinical populations is the paucity of validated tools to evaluate common neurologic symptoms, and ongoing development and validation of such tools is needed to advance the study of—and treatments to improve—HRQL.

This was a survey-based study of a predominantly female and White population at a single academic medical center, albeit a referral center for the surrounding 5 state regions (Utah,

Idaho, Wyoming, Montana, western Colorado, and much of Nevada), for patients with CVID. The overall response rate to the survey was 54.1%, which raises possible concerns about bias and overreporting of symptoms in this study. The demographics of our total population vs responders were similar (female 68% total vs 73.1% responders, age 49.9 years total vs 51.3 years responders). We cannot exclude the possibility that people who responded to the survey were more likely to have symptoms than those who did not respond. Of note, survey response rates have declined in recent years, and email-based surveys may have worse response rates than paper—a consideration for future studies.⁴⁰⁻⁴² The screening survey we used is unvalidated and broad; we used validated surveys for specific symptoms when available, but future work is needed to better understand how the broad symptoms reported in this study may relate specifically to patients with CVID. Our study did not involve a clinical examination or evaluation of reported neurologic symptoms and did not include longitudinal follow-up to further explore the response of symptoms to treatment of CVID or symptomatic management. In addition, it did not attempt to classify patients with CVID based on clinical subtype or comorbidities to further understand the association of neurologic symptoms with the disease process. Future studies to better address these questions are warranted.

People living with CVID report a marked burden of neurologic symptoms, have more sleep disturbance and fatigue, and similar levels of cognitive symptoms as seen in people with established neurologic diseases. The association of these symptoms with clinical subtypes and response to treatment has not yet been established. Clinicians should screen patients with CVID for the presence of neurologic symptoms and offer referral to neurologists and/or symptomatic treatment, given the impact of neurologic symptoms on HRQL. In patients experiencing serious or recurrent infections, neurologists should consider screening for immunodeficiency before initiating medications, which may affect immune responses. Additional research to recognize, characterize, and treat neurologic symptoms is warranted to improve the quality of life of people living with CVID.

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Disclosure

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disclosures relevant to the manuscript but received fellowship funding from the T Siegel Rare Neuroimmune Association (SRNA) and worked on the manuscript then; L. Millsap reports no disclosures relevant to the manuscript; M.M. Paz Soldán, M.M. Cortez, J. Rose, J.E. Greenlee, and A.V. Gundlapalli report no disclosures relevant to the manuscript; H.R. Hill is on the speaker's bureau for Horizon Therapeutics, which makes interferon gamma; K. Wong reports no disclosures relevant to the manuscript; S.L. Clardy received grant funding from the Immune Deficiency Foundation. Go to Neurology.org/NN for full disclosures.

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Continued

Appendix (continued)

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