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DESCRIBING THE SELF-REPORTED COGNITIVE AND EMOTIONAL FUNCTIONING OF ADULT PATIENTS WITH UREA CYCLE DISORDERS

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***ABSTRACT* – Objective:** This study aims to describe the self-reported cognitive and emotional functioning in adult patients with late-onset urea cycle disorders (LO UCDs), highlighting the neuropsychiatric burden of the condition.

Materials and Methods: An observational, retrospective, archival, multicenter study was conducted on 11 female patients' medical records aged 21.5-41 years. Data were extracted from the psychodiagnostic evaluation conducted during routine clinical practice. The psychodiagnostic assessments included the Adult Self-Report (ASR/18-59), the State-Trait Anxiety Inventory – Form Y (STAI-Y), and the Beck Depression Inventory – Second Edition (BDI-II). Descriptive statistics were applied to analyze the findings.

Results: Adult LO UCD patients exhibited significant challenges in emotional and cognitive functioning, with frequent self-reported symptoms related to both cognitive and emotional functioning. Pathological levels of internalizing behaviors, particularly withdrawal, were observed, as well as a high prevalence of self-reported cognitive dysfunction, such as attention problems and lethargy, anxiety and depressive symptoms. Externalizing issues were present but less prevalent. Anxiety and depressive symptoms were also commonly reported, with depressive symptoms impacting both somatic and cognitive domains.

Conclusions: This study underscores the high prevalence of cognitive and emotional dysfunctions in adult LO UCD patients. Future research involving larger cohorts and the combined use of self-report measures and objective neuropsychological assessments is essential to better understand and manage the cognitive and emotional impacts of UCDs.

Keywords: Urea cycle disorders, Behavioral disorders, Cognitive problems, Anxiety, Depression.

Abbreviations: AD_H_prob_T: Attention Deficit/Hyperactivity Problems (T-score); ASEBA: Achenbach System of Empirically Based Assessment; ASR: Adult Self-Report (part of the ASEBA system); BDI-II: Beck Depression Inventory - Second Edition; BDI_FC_p: Beck Depression Inventory Cognitive Factor (percentile score); BDI_SA_p: Beck Depression Inventory Somatic-Affective (percentile score); EO: early-onset; EXT_prob_T: Externalizing Problems (T-score from ASR/18-59); INT_prob_T: Internalizing Problems (T-score from ASR/18-59); IQR: interquartile range; LO: late-onset.

INTRODUCTION

Urea cycle disorders (UCDs) are a set of rare inherited metabolic conditions concerning dysfunctions of urea cycle proteins, which are responsible for removing excess ammonia from the body[1]. Such urea cycle dysregulation affects the detoxification processes of ammonia to urea conversion. Consequent ammonia accumulation in the brain and other tissues, together with the increase of glutamine levels, causes astrocyte swelling and cytotoxic brain edema[2].

UCDs are often diagnosed during the newborn period; however, it is important to highlight that three UCDs [N-acetylglutamate synthase (NAGS), Carbamoyl phosphate synthetase 1 (CPS1), and ornithine transcarbamylase deficiency (OTC) deficiencies] are not detectable through newborn screening. Therefore, UCD cases have also been identified in later childhood or adult age with mild or isolated psychiatric symptoms[3,4]. Early-onset disease (EO) is defined as when hyperammonemia is diagnosed prior to 28 days of age. Individuals often present with life-threatening symptoms, a high risk of mortality and poor neurological outcome in case of survival[5,6]. Otherwise, late-onset disease (LO) is diagnosed when individuals present with symptoms after the newborn period, whose phenotype is variable and typically less severe than in individuals with EO[7,8].

Specific extent and duration of hyperammonemia have been reported to have a crucial impact on cognitive functioning[9]. This results in specific patterns of neurological deficiencies in EO cases, including impaired motor capacity and speed, difficulties in non-verbal intelligence, visual memory and attention deficit[10]. In contrast, LO individuals typically show IQ in the normal range, but may exhibit difficulties in motor planning and executive functioning could be observed[11].

Presumably, as a result of neurological perturbations or the experience of having a chronic illness[12], behavioral and emotional difficulties have also been noticed, including both internalizing (e.g., anxiety, depression, and withdrawal) and externalizing symptoms (e.g., aggression and conduct issues)[10], attention-deficit/hyperactivity disorder and behaviors associated with autism spectrum disorder[12]. Attention problems, dysphoric emotionality, followed by dissocial behavior and difficulties in the management of self or social relationships, can interfere with family life and may impact patients' quality of life[13].

The treatment of UCDs involves a diet with reduced protein intake and pharmacological treatment with ammonium chelating drugs.

Investigations of behavioral disorders in UCD patients, during both diagnostic and therapeutic phases, appear, therefore, to be important. Moreover, compared to children and adolescents, the cognitive and behavioral complications of UCD diagnosis and management have been poorly investigated in adult patients.

Accordingly, we conducted a multicenter, retrospective, observational study utilizing archival data to examine the impact of late-onset UCDs (LO UCDs) on self-reported cognitive and emotional functioning in adult patients affected by LO UCDs who underwent routine psychodiagnostic evaluation at the involved centers, aiming to fill the gap in current knowledge.

MATERIALS AND METHODS

Setting and Patients

An observational, retrospective, archival, multicenter study was carried out between May and June 2025 at IRCCS – Istituto Giannina Gaslini (Genova) and Azienda Ospedaliero Universitaria Policlinico "G. Rodolico – San Marco" (Catania). The study received ethical approvals from the Institutional Review Board of IRCCS Istituto Giannina Gaslini (protocol number 0033844/2024) on 22/10/2024 and from the Comitato Etico Locale Catania 1 - Azienda Ospedaliero Universitaria Policlinico "G. Rodolico – San Marco" - Catania (protocol number 0015160/2025) on 10/03/2025. The study was performed in accordance with the revised version of the Declaration of Helsinki.

Following the receipt of ethical approval, eleven adult female patients diagnosed with LO UCDs were identified at the two participating centers. Patients were included in the study if they met the following criteria: diagnosis of UCDs in childhood and being adults at the moment of the psychodiagnostic assessments. All identified patients had previously undergone comprehensive psychodiagnostic assessments as an integral part of their routine clinical care. Subsequently, these individuals were contacted to inform them about the study's objectives and to obtain their explicit informed consent for the retrospective use of their existing clinical data, which had already been documented in their medical records, solely for research purposes.

Materials/Instruments

Psychodiagnostic assessment comprised three self-report questionnaires. The Adult Self-Report/18-59 (ASR/18-59), part of the Achenbach System of Empirically Based Assessment (ASEBA)[14], is a self-report tool designed to evaluate a wide array of emotional, behavioral, and cognitive issues in adults aged 18-59 years. The ASR/18-59 assesses both general functioning and specific problem behaviors, providing insights into an individual's psychological well-being, interpersonal functioning, and potential psychopathology.

Broadband Scales

- Total Problems: represents the overall level of problem behavior and emotional distress, encompassing all items from each ASR/18-59 problem scale;
- Internalizing Problems: aggregates scores from anxious/depressed, withdrawn, and somatic complaints subscales, reflecting internalized symptoms like anxiety, social isolation, and psychosomatic complaints;
- Externalizing Problems: composed of the aggressive behavior and rule-breaking behavior subscales, this scale captures outwardly directed behaviors, including impulsivity, hostility, and defiance of social norms.

Syndrome scales are empirically derived categories that evaluate specific types of behavioral and emotional difficulties:

- Anxious/Depressed: measures symptoms such as pervasive sadness, anxiety, and worry
- Withdrawn: assesses social disengagement and a preference for isolation
- Somatic Complaints: includes physical symptoms related to psychological distress, such as chronic pain or fatigue
- Aggressive Behavior: captures hostile or confrontational behaviors, including physical and verbal aggression
- Rule-Breaking Behavior: focuses on behaviors indicating a disregard for rules, often associated with impulsivity
- Intrusive: measures socially intrusive and impulsive behaviors, which may disrupt social interactions
- Attention Problems: evaluates difficulties in maintaining concentration and task focus, reflecting issues with distractibility
- Thought Problems: assesses unusual thought patterns and perceptual disturbances that may suggest psychotic-like symptoms or obsessive thinking

Additional Scales

Sluggish Cognitive Tempo: reflects symptoms associated with a slower mental pace, such as lethargy and daydreaming, which can affect attention and motivation

Attention deficit/hyperactivity problems: measures symptoms associated with ADHD, including impulsivity and hyperactivity, which may affect social and occupational functioning.

The State-Trait Anxiety Inventory – Form Y (STAI-Y)[15,16] is a validated self-report measure commonly employed to assess anxiety in both clinical and research settings, differentiating between state anxiety and trait anxiety.

- State Anxiety: measures a transient emotional state, capturing the individual's experience of anxiety in response to specific situations or stress-inducing events. This subscale assesses how anxious the individual feels at a particular moment, influenced by external or immediate factors.
- Trait Anxiety: evaluates a stable personality characteristic, reflecting the individual's general tendency to perceive various situations as threatening or stressful over time. It measures an enduring predisposition toward anxiety.

The Beck Depression Inventory - Second Edition (BDI-II) is a self-report instrument designed to assess the severity of depressive symptoms in adolescents and adults aged 13 years and older[17,18]. Structured to capture both a Total Scale score and two primary factors of depression – Somatic-Affective and Cognitive, the BDI-II assesses a comprehensive range of depressive symptoms, capturing cognitive, affective, and somatic dimensions and consists of 21 items, each reflecting a specific symptom of depression (e.g., sadness, pessimism, fatigue, and sleep disturbances).

Data Analysis

Data analyses were conducted *via* the R Studio software (Vienna, Austria), using descriptive statistics. Given the small sample size, the median value was chosen as a measure of central tendency, while the interquartile range (IQR) was chosen as a measure of dispersion. Categorical variables were reported as absolute frequency and percentage.
Further details have been reported in the Supplementary Material.

RESULTS

The sample comprised eleven adult female patients with LO UCDs. The median age of the patients was 26 years (IQR: 21.5-41 years), with the onset of symptoms ranging from 6 months to 40 years. All patients, except one, were born before the implementation of the newborn screening program in Italy. At the time of the evaluation, all patients were undergoing both pharmacological therapy (ammonium chelating drugs) and a protein-restricted diet. Symptoms presented at onset included: refusal of high-protein foods, vomiting, headache, hypertransaminasemia, episodes of lethargy, coma during pregnancy, mental confusion, hyperammonemia, mild psychomotor retardation (present in only three cases), asthenia, drowsiness, abdominal pain, and coagulation alterations. The specific types of UCDs present in the cohort were: carbamoyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, citrullinemia (argininosuccinate acid synthetase deficiency), argininosuccinate lyase deficiency, argininemia (arginase deficiency), and hyperornithinemia–hyperammonemia–homocitrullinuria syndrome.

ASR/18-59 Questionnaire

According to the ASR/18-59 questionnaire (Table 1 and Figure 1), the median T-score on the Total Problems scale was 60 (IQR: 57.5-70), with five patients (45%) exceeding the pathological threshold. On the Internalizing Problems scale, the median T-score was 63 (IQR: 53-68.5), with five patients (45%) scoring above the threshold. In contrast, the Externalizing Problems scale had a median T-score of 60 (IQR: 57.5-64.5), with three patients (27%) scoring in the pathological range.

Table 1. Median scores for the 11 patients from the scales of the ASR questionnaire.

ASR questionnaire scales	Median (IQR)	Patients above pathological threshold, n (%)
Total Problems	60 (57.5-70)	5 (45%)
Internalizing Problems	63 (53-68.5)	5 (45%)
Externalizing Problems	60 (57.5-64.5)	3 (27%)
Anxious Depressed	61 (54-66.5)	3 (27%)
Withdrawn	65 (59-74)	6 (55%)
Somatic Complaints	53 (52.5-59)	0 (0%)
Thought Problems	51 (50-58)	0 (0%)
Attention Problems	62 (60-74)	5 (45%)
Aggressive Behaviour	61 (56-67)	5 (45%)
Rule-Breaking Behavior	58 (53-61)	1 (9%)
Intrusive	53 (50-57)	1 (9%)
Attention Deficit Hyperactivity Problems	65 (54-74)	6 (55%)
Sluggish Cognitive Tempo	67 (60-73)	6 (55%)

T-scores ≥65 are considered in the pathological range.

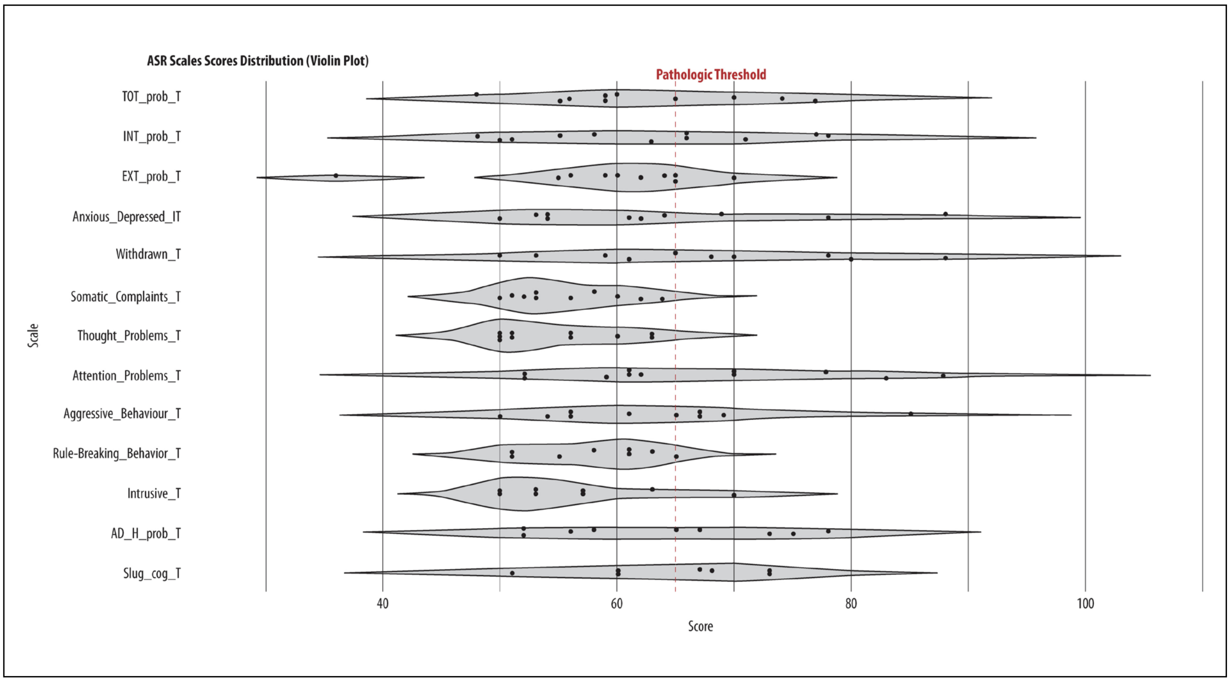

Figure 1. ASR/18-59 scales T scores distribution (Violin plot).

More specifically, regarding the Internalizing Problems sub-scales, the following results were obtained. On the Anxious/Depressed scale, the median T-score was 61 (IQR: 54-66.5), with three patients (27%) scoring above the pathological threshold. The Withdrawn scale showed a higher proportion of patients exceeding the clinical threshold, with six patients (55%) scoring in the pathological range, while the median score was 65 (IQR: 59-74). In contrast, no patients (0%) exceeded the clinical threshold in the Somatic Complaints scale, where the median score was 53 (IQR: 52.5-59).

Regarding the Externalizing Problems sub-scales, for the Aggressive Behavior scale, five patients (45%) reported clinically elevated scores, and a median score of 61 (IQR: 56-67). One patient (9%) scored pathologically on the Rule-Breaking Behavior scale with a median score of 58 (IQR: 53-61). Additionally, one patient (9%) showed a pathological score on the Intrusive scale and a median score of 53 (IQR: 50-57).

Concerning the two remaining sub-scales, in the Attention Problems scale, five patients (45%) reported clinically significant scores, with a median T-score of 62 (IQR: 60-74). However, none of the patients (0%) exceeded the clinical threshold in the Thought Problems scale, where the median score was 51 (IQR: 50-58) (Figure 1).

DSM-Oriented Scales

Regarding the additional DSM-oriented scales, on the Attention Deficit/Hyperactivity Problems scale, the median T-score was 65 (IQR: 54-74), with six patients (55%) exceeding the clinical threshold. Similarly, six patients surpassed the threshold on the Sluggish Cognitive Tempo scale, with a median score of 67 (IQR: 60-73) (Figure 1).

State-Trait Anxiety Inventory – Form Y

Regarding the STAI-Y (Table 2 and Figure 2), on the State Anxiety scale, the median T-score was 48 (IQR: 45.5-70.5), with four patients (36%) exceeding the clinical threshold. Similarly, on the Trait Anxiety scale, four patients (36%) also exceeded the threshold, with a median T-score of 63 (IQR: 45.5-76) (Figure 2).

Table 2. Scores for the 11 patients obtained from the STAI-Y and BDI-II scales.

STAI-Y and BDI-II scales	Median (IQR)	Patients above pathological threshold, n (%)
STAI-Y State Anxiety scale T scores	48 (45.5-70.5)	4 (36%)
STAI-Y Trait Anxiety scale T scores	63 (45.5-76)	4 (36%)
BDI-II Full scale percentile scores	80 (60-99)	5 (45%)
BDI-II Somatic-Affective subscale percentile scores	70 (65-88.5)	5 (45%)
BDI-II Cognitive Factor subscale percentile scores	80 (60-99)	5 (45%)

T-scores ≥65 or percentiles ≥85 are considered in the pathological range.

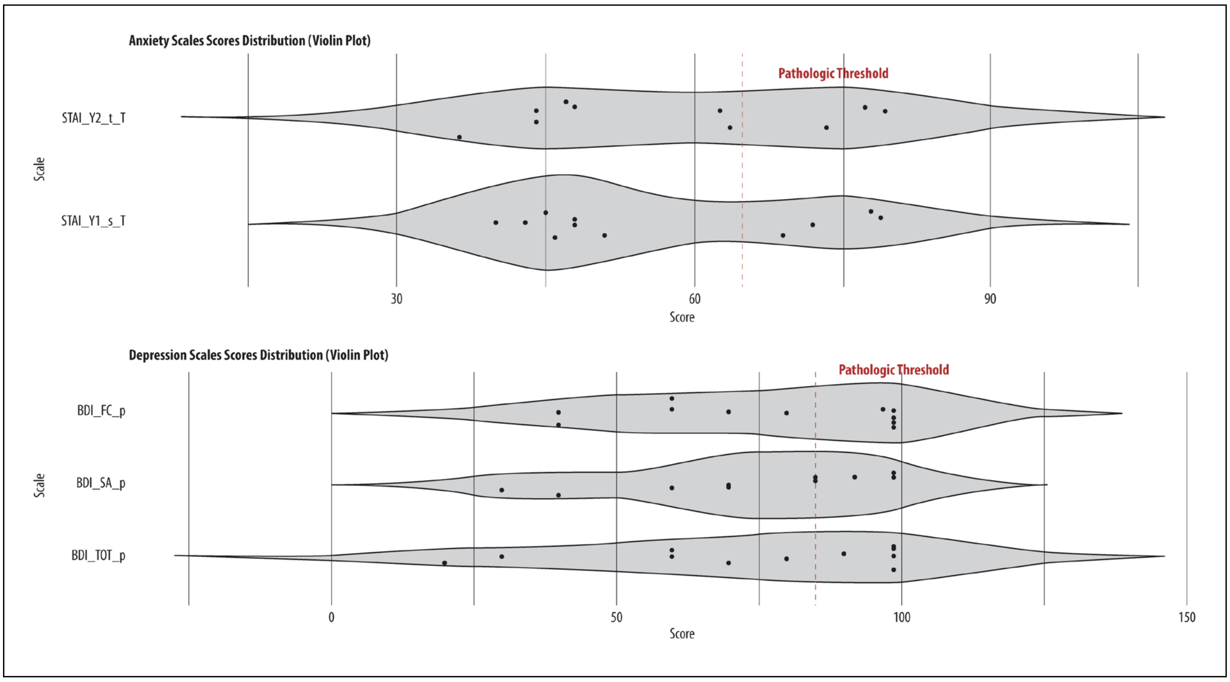

Figure 2. STAI-Y (above) and BDI-II (below) scales scores distribution (Violin plot).

Beck Depression Inventory - Second Edition (BDI-II)

Finally, based on the self-reported BDI-II (Table 2 and Figure 2), the median Total BDI-II score was 80 (IQR: 60-99), with five patients (45%) scoring above the pathological threshold of 85. Among these, four patients exceeded the threshold on both the Somatic-Affective subscale and the Cognitive Factor subscale. One patient surpassed the threshold on the Total BDI and the Cognitive Factor subscale (score: 99) but not on the Somatic-Affective subscale (score: 70). Additionally, one patient exceeded the threshold on the Somatic-Affective subscale (score: 85) while remaining below the threshold on both the Total BDI (score: 80) and the Cognitive Factor subscale (score: 80). More specifically, the median percentile for the Somatic-Affective subscale was 70 (IQR: 65-88.5), with five patients (45%) scoring above 85. Similarly, on the Cognitive Factor subscale, five patients exceeded the threshold, with a median score of 80 (IQR: 60-99) (Figure 2).

DISCUSSION

This study aimed to shed light on the cognitive and emotional impacts of LO UCDs in adults, a condition characterized by high variability in presentation and challenging management across the lifespan. Consistent with previous literature that identifies substantial psychosocial and cognitive impairments in metabolic disorders[10,11], we observed widespread emotional and behavioral disturbances among patients with LO UCDs. In this sample, 45% of patients scored above the clinical threshold on the Total Problems scale of the ASR/18-59, indicating a substantial emotional burden. This aligns with previous findings highlighting how neurological perturbations and the experience of having a chronic illness can be associated with heightened emotional dysregulation and behavioral issues[12].

The Internalizing Problems scale, which captures key symptoms of anxiety, depression, and withdrawal, was clinically significant in 45% of patients, reinforcing the notion that patients with LO UCDs experience heightened social isolation, anxiety, and depressive symptoms as the disease progresses[19,20]. Withdrawal symptoms, particularly prominent in our study (55% above the clinical threshold), suggest a distinct tendency towards social disengagement, which has been documented in the literature as a response to chronic illness-related stressors and decreased quality of life[19]. Despite these findings, only 27% of patients met clinical thresholds for anxious/depressed syndrome scale of ASR/18-59 specifically, and no patients exceeded the threshold for somatic complaints, suggesting that somatic symptoms may be less central to the UCDs experience. This pattern highlights that emotional burdens in UCD patients may manifest more distinctly in social and internalized patterns rather than physical symptoms.

On the Externalizing Problems scale, fewer patients reported clinically significant issues, with only 27% exceeding the threshold. Aggressive behavior was reported in 45% of patients, whereas other externalizing issues, such as rule-breaking and intrusive behaviors, were infrequent. These patterns may reflect a tendency for behavioral dysregulation to manifest more as internalizing than externalizing symptoms in adult UCD patients.

Furthermore, attention deficits, reported by 45% of the sample, represent another prominent aspect of UCD symptomatology, which is consistent with the documented neurotoxic impact of hyperammonemia on cognitive functions, especially attention and executive processes[9]. Complementary assessment with the ADHD and Sluggish Cognitive Tempo subscales further confirmed that five patients experienced clinically significant mental slowing, impulsivity, and inattention. These findings align with prior research highlighting the susceptibility of cognitive functions to metabolic disruptions, especially attentional regulation, as ammonia accumulation impacts the prefrontal cortex and other neural areas responsible for executive functioning[11].

Anxiety and depressive symptoms were further assessed through the STAI-Y and BDI-II scales, where 36% of patients reported both state and trait clinically significant anxiety, and 45% reported depressive symptoms, underscoring the psychological toll of the disorder. Interestingly, four patients exhibited elevated scores on both the somatic-affective and cognitive subscales of the BDI-II, suggesting depressive symptoms in metabolic disorders can encompass both physical and cognitive dimensions.

Moreover, at the time of the evaluation, all patients were undergoing both pharmacological therapy (ammonium chelating drugs) and a protein-restricted diet. Collectively, our findings underscore the intricate link between cognitive impairments and emotional dysfunctions in adult LO UCD patients, with a notable prevalence of attention deficits, anxiety, depression, and social withdrawal. Such impairments are not only compromising individual productivity and quality of life but also affecting family members and the broader social network[13]. The critical need for early identification and integrative, multidisciplinary approaches to address the cognitive and emotional challenges in UCD patients is evident, and our results underline that systematic psychological screening using validated tools should be integrated into the routine clinical care of adult LO UCD patients. This would facilitate early identification of neuropsychiatric issues, allowing for timely intervention and ongoing monitoring of their progression and response to treatment.

The limitations of this study, particularly its small sample size, warrant larger investigations to validate these findings. The study included exclusively females, which may limit the generalizability of the findings to male patients, given the potential for gender-related differences in cognitive and emotional functioning. Moreover, the cognitive aspect of the study is based solely on self-reported questionnaires, which may introduce subjectivity. While these instruments offer useful subjective data, they are inherently limited by potential bias and do not fully capture the complexity of patients' cognitive and neuropsychological functioning. Therefore, incorporating objective neuropsychological assessments is strongly recommended in future studies to improve the comprehensiveness and accuracy of cognitive assessment. Also, future studies should consider the influence of socio-demographic variables, such as educational and socioeconomic status, to deepen the understanding of the factors shaping cognitive and emotional functioning in this population.

CONCLUSIONS

In this study, adult patients with LO UCDs reported self-perceived cognitive impairments, such as attention deficits, alongside emotional issues, including anxiety, depression, and social withdrawal, underscoring the neuropsychiatric burden of UCDs. Future investigations should include larger patient cohorts and incorporate socio-demographic factors (e.g., educational attainment, socioeconomic status) along with objective neuropsychological assessments to enhance our understanding of the cognitive and emotional implications of UCDs in adulthood.

Artificial Intelligence-Assisted Technologies:

No artificial intelligence-assisted technologies were used in the production of this article.

Authors' Contributions:

Study conception and design: PC and GMTL; data collection and analysis: PC, GMTL, MCS, SP, FNP, CV, CM, ACA and MR; manuscript drafting: PC and GMTL; manuscript editing: SP, MCS, CV, FNP, CM, ACA, and MR; correspondence with Comitato Etico Locale Catania 1: CM; approval to submit: PC, GMTL, MCS, SP, FNP, CV, CM, ACA and MR.

Availability of Data and Material:

All data generated or analyzed during this study are included in this published article and its supplementary material.

Conflicts of Interest:

The authors declare that they have no conflict of interest to disclose.

Ethics Approval:

The study received ethical approvals from the Institutional Review Board of IRCCS Istituto Giannina Gaslini (protocol number 0033844/22-10-2024) and from the Comitato Etico Locale Catania 1 - Azienda Ospedaliero Universitaria Policlinico "G. Rodolico – San Marco" - Catania (protocol number 15160/10-3-2025).

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