Received: 25 August 2021 | Revised: 12 November 2021 | Accepted: 7 December 2021

DOI: 10.1002/jimd.12464

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Neuromuscular conditions and the impact of cystine-depleting therapy in infantile nephropathic cystinosis: A cross-sectional analysis of 55 patients

Katharina Vill[1] | Wolfgang Müller-Felber[1] | Timotheus Landfarth[2] | Christian Köppl[3] | Nadine Herzig[4] | Christine Knerr[3] | Heike Holla[6] | Günther Steidle[3] | Erik Harms[5] | Katharina Hohenfellner[6] | the Interdisciplinary Cystinosis Group

[1]Department of Pediatric Neurology and Developmental Medicine, Dr. von Hauner Children's Hospital, LMU – University of Munich, Munich, Germany

[2]Institute for Medical Information Processing, Biometry, and Epidemiology, LMU – University of Munich, Munich, Germany

[3]Kliniken Südostbayern, SPZ, Traunstein, Germany

[4]Schoen Clinic Munich Harlaching, Specialist Centre for Paediatric and Neuro-Orthopaedics, Munich, Germany

[5]Formally Chairman (retired) of the Department of Pediatrics, University of Muenster, Münster, Germany

[6]Department of Pediatric Nephrology, Children's Hospital Rosenheim, Rosenheim, Germany

Correspondence
Katharina Vill, Department of Pediatric Neurology and Developmental Medicine, Dr. v. Hauner Children's Hospital, LMU – University of Munich, 80337 Munich, Germany.
Email: katharina.vill@med.lmu.de

Communicating Editor: Olaf Bodamer

Abstract

Infantile nephropathic cystinosis (INC) is a rare lysosomal storage disease caused by biallelic mutations in the cystinosin gene, leading to cystine accumulation in various organs. The aim of this cross-sectional study was to investigate neuromuscular complications in a cohort of 55 patients (aged 2.8-41.3 years, median 18.5 years) with INC. Clinical examination, jumping mechanography, clinical neurophysiology, and muscle/nerve ultrasound were performed. Physical performance, measured by mechanography, was below average in all patients. However, this reduction in physical performance was not always detected by conventional muscle power assessment. Twenty-eight percent of patients had mostly mild axial weakness of the neck flexors and/or of the abdominal rectus muscles, the latter often presenting during childhood. One adult patient had generalized muscle weakness. Two patients had evidence of specific neuromuscular conditions, which may not have been directly related to cystinosis. 30% of patients presented with mild, 7% with moderate, and 5% with severe weakness of the intrinsic muscles of the hand. Muscle wasting was more pronounced in the older cystinosis patients with multiple organ complications. Sonographic increase in muscle echogenicity corresponded only with severe weakness. Electromyography of the intrinsic hand muscles, performed in selected patients, showed myopathic, neurogenic, or mixed myopathic-neurogenic abnormalities. A particularly important finding of this study is that the neuromuscular complications were largely independent from both the age of initiation of pharmacological cystine-depleting therapy and from adherence to treatment. Significant correlation was observed between better physical performance in jumping and cysteine levels in leukocytes.

KEYWORDS
distal myopathy, Esslinger Fitness Index, infantile nephropathic cystinosis, median nerve, neuromuscular complications

Synopsis
In infantile nephropathic cystinosis, a large proportion of patients are affected by neuromuscular complications due not only to myopathic but also to neurogenic etiology, which are not necessarily dependent on treatment adherence.

1 | INTRODUCTION

Infantile nephropathic cystinosis (INC) is a rare autosomal recessive disease, caused by mutations in the cystinosin (*CTNS*) gene which encodes for the lysosomal cystine transporter cystinosin.[1–3] The lysosomal accumulation of cystine damages the kidneys, eyes, liver, thyroid, pancreas, musculoskeletal system, and central and peripheral nervous systems.[4–7] Patients with INC usually present during the first 2 years of life (mean age 14 months), due to dysfunction of proximal tubules and manifestations of De Debré Fanconi syndrome.[8–10] Clinical symptoms at diagnosis result from extensive electrolyte and bicarbonate losses and include polyuria, dehydration, failure to thrive, developmental delay, and rickets.[11]

Renal replacement therapy first took place for a patient with cystinosis in 1968, with drug therapy subsequently being introduced in the 1980s, allowing patients with INC to survive into adulthood. Cysteamine, the only currently available pharmacotherapy, depletes cells of cystine and delays renal function impairment, with the therapeutic goal of preventing nonrenal complications.[8–10,12]

Evidence of myopathy and cystine storage in the muscles of a patient with nephropathic cystinosis was first demonstrated in 1987.[13] Neuromuscular involvement is now known to be a common extrarenal complication in cystinosis.[14] Swallowing dysfunction is frequently reported,[6] along with extraparenchymal restrictive lung disease that leads to pulmonary dysfunction.[15] In addition, distal muscle wasting and weakness have been observed in approximately one quarter of patients with INC following renal transplantation.[16,17] While a review by Elmonem et al. in 2016 states that "myopathy generally affects patients from their second decade of life,"[18] very little is known about the pathogenesis, predilection, and specific age of onset of muscular weakness in INC, although muscle dysfunction and severity of swallow dysfunction have been previously shown to positively correlate with the number of years without cysteamine therapy.[19]

The aim of this study was to investigate neuromuscular manifestations of INC in a large cohort of patients and to assess the impact of cystine-depleting therapy.

2 | METHODS

2.1 | Design, participants, and assessments

Over a 15-month period (January 2018-March 2019), 55 patients with INC were included in the study. Clinical assessment and data collection took place in the context of a multidisciplinary cystinosis clinic, in which the patients were offered an extensive neurological examination.

Clinical examination of muscle strength was assessed always by the same investigators, experienced in the field of neuromuscular diseases, using the Medical Research Council (MRC) scale (specifically trunk flexion, neck flexion, shoulder abduction, elbow extension and flexion, finger extension and flexion, thumb opposition, intrinsic hand muscle power, ankle extension, and flexion). Time to rise from a lying position was used to evaluate proximal leg muscle power. Involvement of distal hand muscles was evaluated using a 4-point scale (0 = not involved, 1 = slight atrophy or weakness, 2 = marked atrophy without weakness or slight atrophy with weakness, 3 = severe atrophy + weakness).

Muscle performance was measured as jumping force using a mechanography platform. The Leonardo Mechanograph GRFP STD system (Novotec Medical GmbH, Pforzheim, Germany) consists of a split ground reaction force platform connected to a computer. The force was analyzed using the Leonardo Mechanography Software Version 4.4. Forty-five patients performed a "single two-legged jump" test, comprising three consecutive jumps. Patients were advised to jump as high as possible while trying to land on their forefeet. The evaluation was carried out using the automatically calculated "Esslinger Fitness Index" (EFI), which provides percentages of age- and sex-specific normative values.[20]

Muscle ultrasound was conducted using a GE LOGIQ e machine (GE Healthcare, Amersham, Buckinghamshire, UK) with a longitudinal transducer and a frequency of 10 MHz. Gain was set at 59 dB, while depth and focus were individually adjusted.

Sonography of musculature was performed on rectus femoris, vastus intermedius, tibialis anterior, gastrocnemius, deltoid, biceps brachii, triceps brachii, adductor longus, gracilis, medial hamstrings, biceps femoris rectus abdominis, lumbar erector spinae muscles, forearm flexors, forearm extensors, and muscles of the thenar eminence. Imaging was evaluated with a visual four-point grading scale using a modified Heckmatt scale.[21]

Neurosonography was performed on the median nerve, using the GE LOGIQ e machine with a longitudinal transducer and a frequency of 16 MHz. Two cross-sectional areas (CSAs) at the level of the pronator teres in the ventral forearm, and at the level of the carpal tunnel were measured (calculation was based on an ellipse formula).

Clinical neurophysiology was conducted according to standard operating procedures. Somatosensory-evoked potentials (SSEPs) following tibial nerve stimulation were registered from the sensory cortex. Sensory and motor neurophysiology were performed on the median nerve. Stimulation for the sympathetic skin response (SSR) was conducted on the right median nerve (wrist) and the signal was taken in the palm of the opposite hand.

Retrospective evaluation from medical records included data on patient age at initiation of cysteamine treatment, adherence to treatment, renal function, and treatment modalities, such as dialysis or transplantation.

Clinical suspicion of manifest oropharyngeal or oesophageal dysphagia was based on increased throat clearing, coughing, gagging, regurgitation and a feeling of pressure behind the sternum and was quantified by PAS Score.[22] Voice changes after eating ("wet voice sound") suggested vocal fold penetration or aspiration. Esophageal dysphagia was confirmed by gastrografin swallow. Oropharyngeal dysphagia was confirmed with fiberoptic endoscopic evaluation of swallowing or swallowing imaging under fluoroscopy.

Two different methods were used to quantify patient adherence to treatment with cysteamine and to create statistically usable variables. In order to correlate the different parameters of the current study with compliance, we needed a single numerical measure. Therefore, we used the Cystine score as described by Nesterova and Gahl.[23] It incorporates time at initiation of treatment, the level of leucocyte cystine depletion and the duration of cystine-depleting therapy. This modified composite compliance scoring system (ranging from 0 to 3) is based on cystine levels measured in leukocytes and assigns a score to each patient for each year of life to calculate a mean individual score. Each patient was given a score for each year of life and a mean individual score was calculated. A score of 0 was attributed for each year if the patient's mean leukocyte cystine level on cysteamine therapy was ≥1.5 nmol cystine/mg protein or if the patient was not taking cysteamine. A score of 0 was also given for each year before the diagnosis of INC. A score of 1 was given if the mean leukocyte cystine value was ≥1.0 and <1.5 nmol, whereas a score of 2 or 3 was given if this value was ≥0.5 and <1 nmol or <0.5 nmol, respectively.

Second, a binary score, based on the history of cysteamine medication continuity was used to determine whether a patients' medication compliance was consistent or not (medication discontinuation "yes"/"no." The cumulative number of years without therapy is shown in Supplementary Table 1. Based on these data, a "medication discontinuation yes/no" score was obtained to distinguish between patients with steady adherence and those without in whom cysteamine drug monitoring was unavailable. Both measures of adherence were correlated with the different neuromuscular performance variables.

2.2 | Analysis

Multivariable linear and logistic regression models were used to examine the effects of the following explanatory variables: (a) cystine level score; (b) therapy discontinuation (yes/no); (c) age at start of medication; and (d) age at time of the study with various continuous (linear regression) and dichotomous (logistic regression) outcome variables. In each multivariable regression model, the effect of each explanatory variable was assessed through a Wald test. The set of outcome variables included the following continuous variables: (a) amplitude of median compound motor action potentials (CMAP); (b) area of median nerve at forearm and wrist; and (c) performance in the single two-legged jump (EFI in percentage of normative data), along with the following dichotomous variables: (a) oropharyngeal dysphagia; (b) esophageal dysphagia; (c) distal hand muscle wasting score (0/1 or higher); and (d) presence of weakness of other muscle groups (yes/no). The variables "distal hand muscle wasting score" and "weakness of other muscle groups" were originally ordinally scaled but were dichotomized due to the small number of observations in some of the ordinal categories.

For the mean of continuous variables, 95% confidence intervals were obtained based on the t-distribution.

The analysis was performed with SSPS and R Development Core Team (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

3 | RESULTS

Fifty-six patients were investigated. The mean age at examination was 20.7 years (median: 18.5 years; range: 2.8-41.3). The mean age at diagnosis was 19.7 months (median 14.5 months; range: 4 days-8 years). Time of diagnosis was not identical with start of treatment (delayed >3 months) in 11/56 (20%) patients. Age at first diagnosis, age at initiation of cystine-depleting therapy, adherence to therapy, and data on renal function and replacement therapy are shown in Supplementary Table 1, which also lists the sporting activity of the patients. Supplementary Table 2 provides the exact values of the clinical and electrophysiological results of all patients.

Patients received different cysteamine formulations depending on their age and availability, for example, cysteamine as chemical substance (cysteamine bitartrate, cysteamine hydrochloride or phosphocysteamin, introduced in Germany in 1985), Cystagon (introduced in Germany in 1997), or Procysbi (introduced in Germany in 2013). Current medication adherence was monitored by the determination of free, nonprotein-bound cystine in leukocytes.

Two patients were excluded from the statistical analyses to avoid bias in arithmetic data: patient number 78 never received cysteamine treatment and patient 82 started cysteamine medication shortly before inclusion in the study.

3.1 | Distal hand muscle involvement

The distal hand wasting score (1 = mild, 2 = moderate, and 3 = severe) demonstrated a mild involvement of distal hand muscles in 17/55 (31.5%) patients, moderate involvement in 4/55 (7.4%) patients, and severe involvement in 3/55 (5.5%) patients. Weakness of intrinsic hand muscles in some cases preceded atrophy.

In the three severe patient cases, ultrasound demonstrated degenerative findings with increased echogenicity of the musculature (Figure 1). Electromyography (EMG) of intrinsic hand muscles was additionally performed in these three patients: myopathic discharge of motor units was identified in one patient, a mixed myopathic/neurogenic pattern was determined in the second patient, and a pure neurogenic discharge reported in the third patient. In one patient with early atrophy, EMG appeared to be normal.

Patient 82 (aged 39 years) showed an asymmetric pattern of weakness resembling a multiplex-type neuropathy, potentially not cystinosis-related, with left hand extension 4/5 MRC, drop hand on the right, and finger extension reduced to 3/5 MRC on both sides.

3.2 | Weakness and atrophy of other muscle groups

Marked muscle weakness was seen in patients 82 and 87, indicating distinct, and potentially not cystinosis-related, neuromuscular conditions. Patient 87 (aged 14 years) showed a limb girdle muscular phenotype and had weakness of the neck flexors (3/5 MRC), abdominal muscles (3/5 MRC), and gluteals and thighs (4/5 MRC). Tiptoe walk and heel walk were both normal, finger spreading, and extension were slightly reduced with 5-/5 MRC, and the rest of the forearm muscles and intrinsic

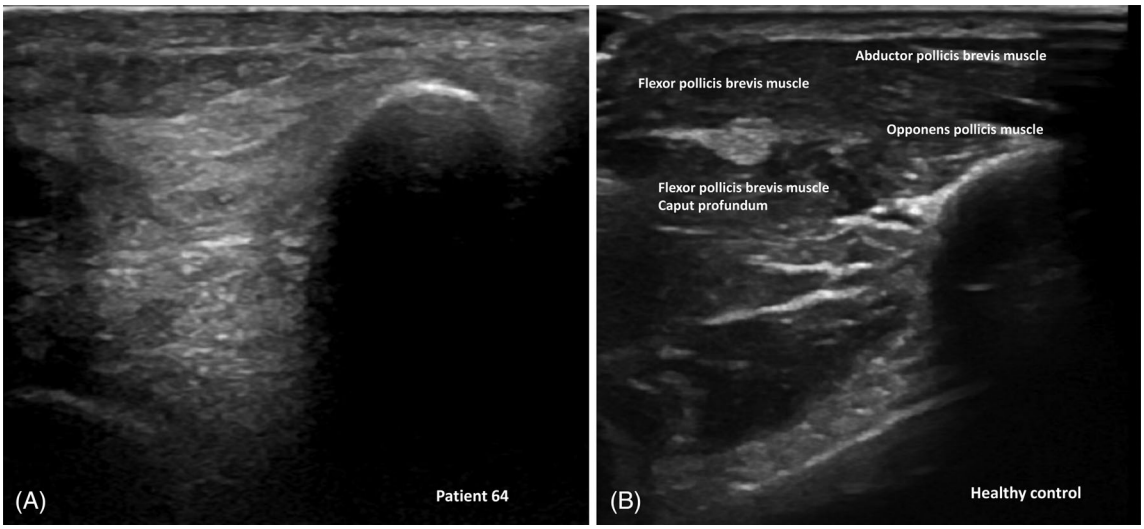

FIGURE 1 (A) Thenar eminence musculature in Patient 64 with clinically severe distal muscle wasting and weakness, with clearly visible increase in echogenicity and decrease of volume. (B) Thenar eminence musculature in a healthy individual aged 44 years

hand muscles showed normal strength. In addition, EMG of the quadriceps muscle was myopathic. The course and clinical picture of this patient suggested in the assessment of the examiners, experienced in neuromuscular diseases in childhood, as well a possible hereditary muscle disease. High-throughput genetic testing (a myopathy-related panel comprising 370 genes) revealed the heterozygous variant c.2359 (p.Arg787Cys) in the *MYH7* gene. The CADD score for the variant is 22.6. Usually, a scaled CADD score of 20 means that a variant is among the top 1% of deleterious variants in the human genome. However, because the occurrence de Novo could not be finally proven (the father is not available for testing, the mother does not carry the variant), the mutation must be considered as variant of unknown significance. Patient 82 (aged 39 years) was unable to walk without support due to ataxia, while muscle function of the legs was normal. Upper extremities showed proximal weakness with shoulder abduction to 3/5 MRC, and elbow flexion and extension 3/5 MRC. The phenotype and neurophysiological findings resembled a multiplex-type neuropathy, while history of painful onset and the rapid progression suggested a cause such as microangiopathy. Laboratory tests revealed elevated serum amyloid and a markedly increased erythrocyte sedimentation rate. Thus, in addition to amyloidosis, an inflammatory cause such as vasculitis had to be considered in a differential diagnosis of this patient in retrospect seems quite likely, since symptoms have responded to dialysis. Unfortunately, we were unable to perform a follow-up examination to document the extent of the reported improvement.

In 17 of the remaining 53 patients (32%), mild to moderate weakness of the axial muscles (abdominals and/or neck flexors) dominated. A 4/5 MRC weakness of the shoulder abductors was identified in two patients, while one patient had 4/5 MRC weakness of the hip flexors. One patient had generalized muscular weakness and died shortly after recruitment into the study.

In 37/53 patients (70%), clinical assessment of muscle groups, other than the intrinsic hand muscles, was completely normal. Nevertheless, mechanography detected reduced physical performance in all investigated patients. The EFI, measured in 44 patients, indicating physical performance by bipedal jump on a mechanography plate in percent (comparison with healthy age and sex peers) was 27% to 92% (median 64%, mean 64%).

3.3 | Muscle ultrasound

Increased echogenicity was seen in the thenar eminence muscles in the three severe cases of hand muscle involvement. Figure 1 shows patient 64's sonographic examination as an example with thenar eminence musculature visibly increased in echogenicity and decreased in volume. In the patient with generalized muscular weakness, echogenicity was increased in the weak muscle groups. Patients 82 and 87 with suspected neuromuscular conditions (however it is also possible that the phenotype of patient 87 with proximal weakness is due to cystinosis, as has occurred in cohorts of other study groups), seemed not inevitably directly related to cystinosis (see above) also demonstrated increased echogenicity of affected muscle groups. The rest of the patients had normal ultrasound findings with no visibly relevant increase in echogenicity.

3.4 | Nerve ultrasound

The CSA of the median nerve at the forearm (level of the pronator teres) in our patients revealed a range of 2.4 to 13.5 mm^2 (mean: 5.5 mm^2; median: 5.4 mm^2; normal range in adults: mean $\pm$ 2 SD = 4.3-10.7 mm^2). Ultrasound of the median nerve at the level of the carpal tunnel revealed a range of 2.9 to 18.8 mm^2 (mean: 8.3 mm^2; median: 7.7 mm^2; normal range in adults: mean $\pm$ 2 SD = 5.0-14.6 mm^2). These findings were largely unremarkable.

3.5 | Somatosensory-evoked potentials

Recordable SSEP results were available in 41 patients. Mean result for P40 latency after stimulation of the tibial nerve was 39 seconds (median: 40 seconds; range: 32-47 seconds). For all patients in whom measurements were possible, SSEP curves were well reproducible and without relevant differences between right and left side.

3.6 | Neurophysiology

Besides patient 82 with suspected multifocal neuropathy, motor and sensory nerve conduction velocities and sensory nerve action potential amplitudes of all other patients were normal. CMAPs of the median nerve were lower than the normal lower limit cut-off of 5 mV in 34/48 measured patients (range for 34 patients: 0.1-4.9 mV; mean: 2.8 mV; median: 2.7 mV; range for all patients except patient 78: 0.1-9.5 mV; mean: 3.8 mV; median: 3.5 mV).

3.7 | Sympathetic skin response

SSR was investigated in 54 patients with no remarkable findings.

3.8 | Dysphagia

In addition to a prolonged oral phase (slow processing of food in the mouth until swallowing and prolonged duration of meals), clinical signs of swallowing problems such as dry mucous membranes in the orofacial and pharyngeal areas that make it difficult to insalivate and swallow food were reported by about 20% of patients and may also be due to medication in parts of them. Impaired oral motor function, that is, a reduction in the strength, coordination, and range of motion of the tongue, lips, jaw, palate, and cheeks, was present in approximately 30% of all cystinosis patients. Those patients in whom a diagnosis of manifest esophageal or oropharyngeal dysphagia could be made clinically or by instrumentation are listed in supplemental Table 2 and were included in the statistical analysis. More orofacial subtleties will be described in a separate publication.

No direct association could be established with regard to the co-occurrence of manifest dysphagia and skeletal or hand muscle weakness. The three oldest patients had both manifest dysphagia and advanced hand muscle weakness, but in the other patients, the respective symptoms occurred independently in approximately half of the respective patient groups (Supplementary Table 2)."

3.9 | Regression analysis of results with age at start of therapy, age at examination, medication adherence score, and medication discontinuation score

Supplementary Table 3 shows the results from linear and logistic (depending on the variable type) regression analysis with explanatory variables and the outcome variables.

Logistic regression analysis of oropharyngeal and esophageal dysphagia (N = 54), logistic regression analysis of the "distal hand muscle wasting score" (n = 54), logistic regression analysis of "weakness of other muscle groups" (n = 53), linear regression analysis of the CSA of the median nerve at wrist and forearm (n = 44), revealed no significant association with medication discontinuation, age at start of cystine-depleting therapy, or current age at the time of the study. For CSA, there was a minimal trend with greater CSA associated with older age; the effect was significant and is consistent with physiological changes with older age.

Linear regression analysis of the median nerve CMAP amplitude (n = 47) demonstrated that if a patient had discontinued medications, with constant conditions of the other variables "age at examination" and "age at therapy start," the CMAP amplitude of the median nerve was on average 2.21 mV lower; this effect was significant.

Linear regression analysis of the EFI in the single two-legged jump (n = 44) revealed a significant association with cystine level score: if the cysteine level score is one unit lower, an improvement in performance of approximately 14% EFI can be expected.

4 | DISCUSSION

We performed a neuromuscular evaluation, including clinical, electrophysiological, and ultrasonographic investigations, on 55 pediatric and adult patients with INC over a 15-month period.

The main objective of this publication is to describe the occurrence of neuromuscular complications of a large cohort of cystinosis patients and our data are intended to contribute to a better understanding of the cause of neuromuscular complications.

The key finding from statistical analysis in this study refers to the influence of cystine depleting therapy with cysteamine. The parameters of hand weakness, muscular weakness outside the palmar musculature, dysphagia, and median nerve thickness remained without measurable influence of the parameters cystine level score, therapy discontinuation, or age at therapy initiation. It could only be shown that an interruption of the therapy over several years causes a reduction of the amplitude of the motor median nerve, but this does not have a statistical effect on the hand score. This is not contradictory, since 2.2 mV is not a major change in CMAP given the variability in normal CMAP amplitude. Although significant, there may be other factors contributing to the CMAP amplitude in healthy and affected patients.

A particularly important new finding from our study is that our entire patient cohort underperformed physically. Performance on a mechanography platform, standardized for age and sex, were lower than average and this was the case even for patients in whom "classical" or "formal" testing using the MRC scale was unremarkable. This already established test[24,25] was chosen instead of a 6-minute walk test, because in the group of cystinosis patients, the majority are ambulatory and can usually complete a 500-m distance without problems. Better therapy compliance as measured by the cysteine level score, increased significantly the expected value of this physical performance.

Further focal proximal muscular abnormalities in our cohort were dominated by a mild axial weakness, which was already present in single pediatric patients. Impaired oral motor function was present in approximately 30% of all cystinosis patients. In 25 patients, a diagnosis of manifest esophageal or oropharyngeal dysphagia was present.

Distal muscle wasting and weakness, so far described as "distal myopathy," usually includes atrophy of the thenar and hypothenar and the intrinsic hand muscles and

are the most frequently described neuromuscular symptom of INC. In our cohort, 30% presented with mild, 7% with moderate and 5%, with severe affection.

The results largely confirm prior research findings regarding the prevalence of distal muscle wasting and weakness in patients with INC. We did not, however, find evidence of the previous assumption of a purely myopathic etiology in this patient group, since, that is, EMG findings differ from previous research[17]: one of our patients with discreet atrophy had a normal EMG, while out of the three severely affected patients, one had a neurogenic, one a mixed, and one a myopathic pattern with early recruitment of low amplitude short duration muscular action potentials on voluntary action. MUP analysis was not performed. We conclude that the distal muscle wasting in cystinosis can have dual (or additional) etiologies; however, of course, we cannot make this assumption based on EMG of four patients only. There are multiple factors and issues with regards to sensitivity of myopathic changes in needle EMG of the study and the pathophysiology of distal muscular wasting in INC remains not fully understood. In previous publications, biopsy of severely affected intrinsic hand muscles, however, available from only two patients, revealed marked fiber size variability, prominent acid phosphatase-positive vacuoles, the absence of neurogenic changes such as fiber type grouping, and the absence of inflammatory myopathy. Crystals of cystine were detected in perimysial cells and the muscle cystine content of clinically affected muscles was markedly elevated.[13,16,17]

We report on two patients whose rather distinctive findings, in our opinion, are not necessarily directly related to the diagnosis of cystinosis: a 39-year-old female patient showed (apart from a myopathic finding in the intrinsic hand musculature) a multifocal, that is, vasculitis-associated neuropathy with rapidly progressive, nonsymmetrical weakness of several muscle groups. She reported improvement after initiation of dialysis. The other patient, a 14-year-old boy, showed proximal muscle weakness with increased echogenicity and myopathic EMG of the thigh. The clinical picture appeared compatible with congenital myopathy or limb girdle weakness. Molecular genetic clarification using next generation sequencing revealed a *MYH7* mutation, which remains a variant of unclear significance due to the inability to genetically test the patient's father, but has a high CADD score and could explain the clinical findings.

Regarding practical conclusions for the treating physicians of INC patients, this work contributes mainly to patient counseling and prognosis assessment. The apparative examinations in terms of regular neurophysiology, neurosonography and myosonography do not seem to be necessary on a regular basis in order to derive a practical benefit for the patients. As an example, muscle remodeling can be observed in myosonography only when clinical symptoms are already advanced. However, if unusual symptoms occur, referral to a neuromuscular specialist should be made.

4.1 | Limitations

The regression analysis that we used estimates the effects (and assesses their significance) of the individual influencing variables on the outcome parameters. This provides a very clean statistic, but the set of influence variables is limited in a cohort of 55 patients, which is large for such a rare disease, but rather small for a statistical analysis. Therefore, with four influencing variables already present, renal function had to be omitted as an influencing parameter, since its complexity could not be statistically formulated as a binary or continuous variable. Basically, it is possible that the occurrence of neuromuscular complications is directly influenced by renal function. Similarly, the role of long-term severe carnitine deficiency in the development of myopathy cannot be excluded. In Germany, cystinosis patients are now substituted with carnitine as standard. However, it can be assumed that not all centers have ensured regular substitution with carnitine in the older patients in this collective, who were among the first patients in Germany to be treated with cysteamine.

5 | SUMMARY

This study makes a major contribution to our understanding of the correlation between the age at disease onset and adherence to drug therapy with neuromuscular symptoms in patients with INC. Our data strongly suggest that medication compliance has only minimal influence on the extent of neuromuscular manifestations. We identified a high prevalence of hand muscle wasting and weakness in our patient cohort, which can have additional etiologies beyond myopathy. Furthermore, neuromuscular involvement was dominated by mostly mild axial weakness, which can be present in childhood and should be addressed therapeutically. The basic physical performance in the whole patient cohort was reduced when compared with the general population using a standardized fitness score (in this case the Esslinger Fitness Score on the Jumping Mechanography Plate). This performance seems to be influenced by good therapy compliance and the finding reflects the effect of this chronic severe illness on muscle performance.

ACKNOWLEDGMENTS

Funding for this study was provided by the Cystinosis Foundation. The authors confirm independence from the sponsors and the content of the article has not been influenced by the sponsors. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Katharina Vill: Conceptualized and designed the clinical study, collected clinical, sonongraphic, and electrophysiological data, and wrote and drafted the initial manuscript. **Wolfgang Müller-Felber**: Conceptualized and designed the clinical study, collected electrophysiological data, and reviewed and revised the manuscript. **Timotheus Landfarth**: Performed the statistical analysis. **Nadine Herzig** and **Christian Köppl**: Performed the mechanography investigations. **Christine Knerr**: Performed the examinations with regard to dysphagia. **Heike Holla**: Compiled the dataset. **Günther Steidle**: Collected clinical data. **Erik Harms**: Gave scientific advice and critically reviewed the manuscript for important intellectual content. **Katharina Hohenfellner**: Co-conceptualized the clinical study, collected clinical data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

All values that were calculated can be found in the supplementary tables. The raw clinical, sonographic, and electrophysiological data, as well as laboratory values and anamnestic data, are documented in the patient files non-anonymized with the treating physicians in München and Rosenheim and cannot be shared freely. The R-code used can be obtained from coauthor T. L. As guarantor for the article, K. V. accepts responsibility for the neuromuscular examinations and data, N. H. and C. K. provided the mechanography data, C. K. provided the oropharyngeal data, K. H. provided renal data and data regarding patient's history and therapy, and T. L. performed the statistical analysis.

ETHICS STATEMENT

The study was approved by the ethics committee of the Bavarian Medical Association (internal No.: 2015-030).

REFERENCES

1. Gahl WA, Bashan N, Tietze F, Bernardini I, Schulman JD. Cystine transport is defective in isolated leukocyte lysosomes from patients with cystinosis. *Science*. 1982;217(4566):1263-1265.
2. Kalatzis V, Cherqui S, Antignac C, Gasnier B. Cystinosin, the protein defective in cystinosis, is a H(+)-driven lysosomal cystine transporter. *EMBO J*. 2001;20(21):5940-5949.
3. Town M, Jean G, Cherqui S, et al. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nat Genet*. 1998;18(4):319-324.
4. Gahl WA, Kaiser-Kupfer MI. Complications of nephropathic cystinosis after renal failure. *Pediatr Nephrol*. 1987;1(3):260-268.
5. Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med*. 2002;347(2):111-121.
6. van Rijssel AE, Knuijt S, Veys K, Levtchenko EN, Janssen MCH. Swallowing dysfunction in patients with nephropathic cystinosis. *Mol Genet Metab*. 2019;126(4):413-415.
7. Servais A, Saitovitch A, Hummel A, et al. Central nervous system complications in adult cystinosis patients. *J Inherit Metab Dis*. 2020;43(2):348-356.
8. Thoene JG, Oshima RG, Crawhall JC, Olson DL, Schneider JA. Cystinosis. Intracellular cystine depletion by aminothiols in vitro and in vivo. *J Clin Invest*. 1976;58(1):180-189.
9. Gahl WA, Reed GF, Thoene JG, et al. Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med*. 1987;316(16):971-977.
10. Markello TC, Bernardini IM, Gahl WA. Improved renal function in children with cystinosis treated with cysteamine. *N Engl J Med*. 1993;328(16):1157-1162.
11. Roth KS, Foreman JW, Segal S. The Fanconi syndrome and mechanisms of tubular transport dysfunction. *Kidney Int*. 1981;20(6):705-716.
12. Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. *Pediatr Nephrol*. 2013;28(1):51-59.
13. Gahl WA, Dalakas MC, Charnas L, et al. Myopathy and cystine storage in muscles in a patient with nephropathic cystinosis. *N Engl J Med*. 1988;319(22):1461-1464.
14. Gahl WA, Balog JZ, Kleta R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann Intern Med*. 2007;147(4):242-250.
15. Anikster Y, Lacbawan F, Brantly M, et al. Pulmonary dysfunction in adults with nephropathic cystinosis. *Chest*. 2001;119(2):394-401.
16. Charnas LR, Luciano CA, Dalakas M, et al. Distal vacuolar myopathy in nephropathic cystinosis. *Ann Neurol*. 1994;35(2):181-188.
17. Vester U, Schubert M, Offner G, Brodehl J. Distal myopathy in nephropathic cystinosis. *Pediatr Nephrol*. 2000;14(1):36-38.
18. Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. *Orphanet J Rare Dis*. 2016;11:47.
19. Sonies BC, Almajid P, Kleta R, Bernardini I, Gahl WA. Swallowing dysfunction in 101 patients with nephropathic cystinosis: benefit of long-term cysteamine therapy. *Medicine*. 2005;84(3):137-146.
20. Busche P, Rawer R, Rakhimi N, Lang I, Martin DD. Mechanography in childhood: references for force and power in counter movement jumps and chair rising tests. *J Musculoskelet Neuronal Interact*. 2013;13(2):213-226.
21. Vill K, Schessl J, Teusch V, et al. Muscle ultrasound in classic infantile and adult Pompe disease: a useful screening tool in adults but not in infants. *Neuromuscul Disord*. 2015;25(2):120-126.

22. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. *Dysphagia*. 1996;11(2):93-98.
23. Nesterova G, Williams C, Bernardini I, Gahl WA. Cystinosis: renal glomerular and renal tubular function in relation to compliance with cystine-depleting therapy. *Pediatr Nephrol*. 2015;30(6):945-951.
24. Blaschek A, Rodrigues M, Rawer R, et al. Jumping mechanography is a suitable complementary method to assess motor function in ambulatory boys with Duchenne muscular dystrophy. *Neuropediatrics*. 2021;52(6):455-461.
25. Vill K, Ille L, Blaschek A, et al. Jumping mechanography as a complementary testing tool for motor function in children with hereditary motor and sensory neuropathy. *Neuropediatrics*. 2017;48(6):420-425.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Vill K, Müller-Felber W, Landfarth T, et al. Neuromuscular conditions and the impact of cystine-depleting therapy in infantile nephropathic cystinosis: A cross-sectional analysis of 55 patients. *J Inherit Metab Dis*. 2022;45(2):183-191. doi:10.1002/jimd.12464