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Author: Amytice Mirchi, Félixe Pelletier, Luan T. Tran, Stephanie Keller, Nancy Braverman, Davide Tonduti, Adeline Vanderver, Federico Roncarolo, Amy Pizzino, Marie-Emmanuelle Dilenge, Chantal Poulin, Michael Shevell, Annette Majnemer, Guillaume Sébire, Myriam Srour, Bradley Osterman, Renée-Myriam Boucher, Michel Vanasse, Elsa Rossignol, John Mitchell, Sunita Venkateswaran, Daniela Pohl, Marcelo Kauffman, Raphael Schiffmann, Cyril Goizet, Sebastien Moutton, Geneviève Bernard

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HEALTH-RELATED QUALITY OF LIFE FOR GENETICALLY DETERMINED LEUKOENCEPHALOPATHY PATIENTS

Amytice Mirchi[1,2,3,4], Félixe Pelletier[1,2,3,4], Luan T. Tran[1,2,3,4], Stephanie Keller[5], Nancy Braverman[1,3], Davide Tonduti[6,7], Adeline Vanderver[8,9], Federico Roncarolo[10], Amy Pizzino[11,12], Marie-Emmanuelle Dilenge[13,14,15], Chantal Poulin[13,14,15], Michael Shevell[13,14,15,16], Annette Majnemer[13,14,15,16], Guillaume Sébire[13,14,15,16], Myriam Srour[13,14,15,16], Bradley Osterman[17], Renée-Myriam Boucher[17], Michel Vanasse[18], Elsa Rossignol[18], John Mitchell[14,16,19,20], Sunita Venkateswaran[21], Daniela Pohl[21], Marcelo Kauffman[22], Raphael Schiffmann[23], Cyril Goizet[24], Sebastien Moutton[24], Geneviève Bernard[1,2,3,4]

1. Department of Medical Genetics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada
2. Departments of Neurology and Neurosurgery, McGill University, Montreal, Canada
3. Department of Pediatrics, McGill University, Montreal, Canada
4. Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montreal, Canada
5. Department of Pediatrics, Division of Pediatric Neurology, Emory University, Atlanta, Georgia, USA
6. Child Neurology Unit, V. Buzzi Children's Hospital, Milan, Italy
7. Child Neurology Department, C. Besta Neurological Institute, Milan, Italy
8. Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
9. Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
10. Institut de recherche en santé publique de l'Université de Montréal, Montreal, Canada
11. Children's Hospital of Philadelphia, Philadelphia, USA
12. MetroHealth Hospital, Cleveland, Ohio, USA
13. Departments of Neurology and Neurosurgery, McGill University, Montreal, Canada
14. Departments of Pediatrics, McGill University, Montreal, Canada
15. Department of Pediatrics, Division of Pediatric Neurology, Montreal Children's Hospital and the McGill University Health Centre, Montreal, Canada

16. Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montreal, Canada

17. Department of Pediatrics, Division of Pediatric Neurology, Centre Hospitalier de l'Université Laval, Québec, Québec, Canada

18. Departments of Neurosciences and Pediatrics, Division of Pediatric Neurology, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Québec, Canada

19. Department of Medical Genetics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada;

20. Department of Pediatrics, Division of Pediatric Endocrinology, McGill University Health Center, Montreal, Quebec, Canada

21. Division of Neurology, Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada

22. Neurogenetics Unit, Department of Neurology, Hospital JM Ramos Mejia and CONICET, Buenos Aires, Argentina

23. Institute of Metabolic Disease, Baylor University Medical Center at Dallas, Dallas, TX, USA

24. Univ. Bordeaux, Laboratoire MRGM, INSERM U1211 and CHU Bordeaux, Service de Génétique Médicale, F-33000 Bordeaux, France

Corresponding author: Geneviève Bernard MD, MSc, FRCPc (genevieve.bernard@mcgill.ca) , Research Institute of the McGill University Health Centre, 1001 boul Décarie, Site Glen Pavilion E / Block E, *CHHD* Mail Drop Point #EM03211 (cubicle C), Montréal, QC H4A 3J1, Canada

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Abstract

AIMS

To characterize health-related quality of life (HRQOL) in patients with genetically determined leukoencephalopathies as it relates to the severity of clinical features and the presence/absence of a precise molecular diagnosis.

METHOD

HRQOL was assessed using the Pediatric Quality of Life Inventory (PedsQL) model (Pediatric Quality of Life Inventory 4.0 Self and Proxy-reports) on 59 patients diagnosed with genetically determined leukoencephalopathies. In total, 38 male and 21 female patients aged from 1 to 32 years (mean 9 years), as well as their parents, completed the PedsQL HRQOL measures. In addition, participants underwent/filled detailed standardized clinical assessments/questionnaires. The correlation between HRQOL results and the severity of the clinical features as well as the presence/absence of a molecular diagnosis was analyzed.

RESULTS

Patients with more severe clinical features showed statistically significant lower total PedsQL scores. More specifically, lower HRQOL was noted in children with sialorrhea, wheelchair use, gastrostomy and dystonia.

INTERPRETATION

In this study, we have shown that patients with more severe clinical features experience a lower quality of life. Our study further highlights the importance of addressing both physical and psychosocial issues and discussing perception of quality of life with both parents and children. A future larger multicenter prospective study will be important to further define the burden of these diseases and identify modifiable factors.

Leukodystrophies (LD) and genetic leukoencephalopathies (gLE) are disorders of the cerebral white matter. LD are defined as primary genetic disorders of the white matter of the brain[1,2]. On the other hand, gLE are disorders where the cerebral white matter involvement is thought to be secondary to a primary neuronal, vascular, systemic or other pathology[1]. Here, we will use the terms genetically determined leukoencephalopathies to include both LD and gLE. Patients with LD and gLE typically experience a progressive course. With next generation sequencing, the percentage of molecularly unsolved cases of LD has decreased significantly from 40-50%[3,4] to as low as 20%[2,3], depending on the cohorts studied. The percentage of molecularly unsolved leukoencephalopathies is higher, likely because of the extensive heterogeneity in diagnoses[5,6].

Quality of Life (QOL) is defined by the World Health Organization as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns[7]". Health-related Quality of Life (HRQOL) refers to an individual's perceived QOL as it relates to their physical and mental health[8]. Models characterizing HRQOL can provide valuable information on core dimensions of health such as physical, emotional, social and scholarly functioning.

To this day, there have been very few studies exploring the impact of genetically determined leukoencephalopathies on patients using standardized questionnaires. Considering that a large proportion of these disorders lead to progressive disabilities and ultimately to premature death, we hypothesized that the degenerative nature of these diseases imposes great emotional burden and stress on patients, leading to a poorer QOL. Assessing HRQOL in this group of patients can contribute to finding ways to

optimize the care of this population; it can help clinicians identify and prioritize problems, facilitate communication, and screen for overlooked problems[9,10]. In this study we assessed HRQOL of genetically determined leukoencephalopathy patients and demonstrated that the overall severity of the disease, as well as the presence of specific features/impairments, lead to a worse HRQOL score.

METHOD

Participants

Fifty-nine participants aged from 1 to 32 years old were recruited between 2014 and 2016 at the Leukodystrophy clinic of the Montreal Children's Hospital of the McGill University Health Center, the Myelin Disorders Clinic at the Children's National Medical Center in Washington DC and at the Foundation of the Carlo Besta Neurological Institute, Milan, Italy. Eligible participants included those diagnosed with a genetically determined leukoencephalopathy, with/without a precise molecular diagnosis. Their unaffected parents were also recruited. This study was approved by the Ethics committees of all above-listed participating institutions. Patients and/or parents gave informed consent to the research study and to publication of the results.

Measurements

HRQOL was assessed using the Pediatric Quality of Life Inventory (PedsQL 4.0) model according to guidelines (Table 1). The PedsQL 4.0 Generic Core Scales[11,12,13] and the PedsQL Multidimensional Fatigue Scales[14,15] were administered once for each of the 59 patients. Self and Proxy-report versions of these questionnaires were completed when possible. Self-report versions measure the children's own perspective of their HRQOL while the Proxy-report versions measure the parents' perspectives of their child's HRQOL. On the questionnaires, responses to items were scaled on a 5-point Likert

Scale from 0 (when responding "Never") to 4 (when responding "Almost always"). For each item, participants had to select an answer from 0 to 4, indicating how much of a problem each item had been for their child/themselves in the past month (see Supplementary Material for sample of item content). Items on the questionnaires were reversed scored and linearly transformed to a 0-100 scale (higher scores representing a better HRQOL). Total HRQOL scores and scale scores were computed for each participant. If more than 50% of the items in a scale had been left unanswered, the scale scores could not be computed as per the PedsQL scoring instructions and therefore, the data from the questionnaire could not be used in our analysis.

Procedure

Participants were asked to complete the PedsQL questionnaires at the time of the clinical data collection or soon after. Data on clinical characteristics was collected using standardized clinical evaluations performed at one of the three participating centers or using a detailed clinical note from the treating neurologist or a Developmental and Medical History Questionnaire completed by the parents.

Statistical analysis

To assess HRQOL, we calculated the mean total HRQOL scores and the mean scale scores related to the severity of the clinical presentation. More specifically, HRQOL was assessed in relation to the presence/absence of the following clinical variables: sialorrhea, wheelchair use, falls, dysphagia, gastrostomy, ataxia, dystonia, dysarthria and seizures. We used T-Tests for independent samples to assess significant differences between HRQOL scores and the presence/absence of these clinical variables. T-Tests were also used to compare the PedsQL 4.0 Generic Core Scales scores of patients with none of the nine clinical features with those with one or more

clinical features. In addition, we analyzed HRQOL in relations to the presence/absence of a precise molecular diagnosis.

The PedsQL 4.0 Generic Core Scale and Multidimensional Fatigue Scale mean scores were compared between the parents Proxy-reports and the child Self-reports in order to assess differences in the perception of HRQOL between the parents and the child. Intraclass correlation coefficients (ICC) were calculated.

RESULTS

Fifty-nine patients were enrolled in this study. As shown in Table 1, the PedsQL 4.0 Generic Core Scales Proxy-reports were completed for 51 participants by one of their parents and the Self-reports were completed by 16 participants. The PedsQL Multidimensional Fatigue Scale Proxy-reports were completed for 39 participants by one of their parents and the Self-reports were completed by 15 participants. Clinical characteristics and molecular diagnoses for our study population are presented in Table 2. Table 3 presents the mean scores and standard deviations of the PedsQL 4.0 Generic Core Scales and the Multidimensional Fatigue Scale Proxy and Self-reports. Some participants are reported twice in the table, once as a Self-report and once as a Proxy-report. Furthermore, the numbers reported in Table 3 do not always reconcile with the total number of participants completing the questionnaires because some of the participants did not entirely complete the questionnaires, possibly due to the complexity of the questionnaires and their lack of specificity for the diseases assessed in this study.

HRQOL in relation to the severity of clinical features

Concerning the PedsQL 4.0 Generic Core Scales Proxy and Self-reports, the mean total scores obtained were lower in the presence of features seen when a severe clinical

involvement was present: sialorrhea, wheelchair use, falls, dysphagia, gastrostomy, ataxia, dystonia, dysarthria and seizures. In this particular patient cohort, the lowest mean total score from the Proxy-reports were reported for patients needing gastrostomy (41.59), followed by patients with dystonia (47.57) and for those needing a wheelchair (47.66). As shown in Table 3, significantly lower mean total scores were obtained on the PedsQL 4.0 Generic Core Scales Proxy-reports in the presence of sialorrhea (P=0.023), wheelchair use (P=0.008), gastrostomy (P=0.031) and dystonia (P=0.003). Regarding the different functioning domains on these Proxy-reports, the lowest scores were found in the physical functioning domain. Concerning the Multidimensional Fatigue Proxy-report, a statistically significant lower mean total score was obtained in the presence of sialorrhea (P=0.007), dysphagia (P=0.02), gastrostomy (P=0.03) and dystonia (P=0.009).

The mean total score for the PedsQL 4.0 Generic Core Scales Proxy-reports for patients with none of the nine clinical features was significantly higher than the score for patients presenting at least one of the nine clinical features previously mentioned (84.03 as compared to 52.35 respectively). This finding was also true when comparing the physical (87.38 versus 40.73), emotional (89.38 versus 64.45) and social (80.83 versus 54.24) functioning scores. Results from T-Tests analysis shown in Table 4 suggest that patients with at least one of the nine clinical features suffer from a poorer HRQOL as compared to patients with none of these features.

Identification of problems most frequently encountered by the genetically determined leukoencephalopathy patient population aged 5 years old and above as reported by their parents

We calculated the frequency of “often” and “almost always” as responses to items on the PedsQL 4.0 Generic Core Scale Proxy-Reports to identify problems most frequently reported by the parents for this patient population. Parents of 31 families (52.5%) with children aged 5 years old and above completed the PedsQL 4.0 Generic Core Scales Proxy-reports. As shown in Table 4, the most frequently reported problems for patients within the physical functioning domain were difficulties with running (67.7%) and walking more than one block (64.5%). In relation to emotional functioning, having trouble sleeping (16.1%) and worrying about what will happen to him/her (16.1%) were the most frequently reported problems. Concerning social functioning, the main problems reported were not keeping up with other adults/teens/children (74.2%) and not being able to do things that others of the same age can do (71.0%).

ICC for Parent-Child concordance

As shown in Table 4, the ICC obtained when comparing the total score of the Multidimensional Fatigue Scale Proxy and Self-reports was 0.876, indicating a strong agreement. On the PedsQL 4.0 Generic Core Scales, ICC values suggesting a strong agreement were obtained when comparing the patients’ and parents’ total scores (0.780) and emotional functioning scores (0.725). However, the ICC obtained for the physical (0.431) and social (0.491) functioning score indicate a moderate agreement only. The mean physical and social functioning scores were lower on the Proxy-reports (45.48 and 56.75 respectively) as compared to those obtained on Self-reports (52.11 and 69.79 respectively).

HRQOL in the presence/absence of a precise molecular diagnosis

When comparing total mean scores of the PedsQL 4.0 Generic Core Scales and the Multidimensional Fatigue Scale, we did not find any statistically significant relationship

between HRQOL and the presence/absence of precise molecular diagnosis. As shown in Table 5, PedsQL 4.0 Generic Core Scales and the Multidimensional Fatigue Proxy and Self-reports scores seemed to be lower in the presence of a precise molecular diagnosis. However, the results obtained are statistically insignificant with P-values well above 0.05 and the number of participants without a precise molecular diagnosis who completed the Self-reports was very small (n=2). Therefore conclusions cannot be drawn from this data.

DISCUSSION

Overall, genetically determined leukoencephalopathy patients seem to have a poorer HRQOL as it relates to the severity of their clinical features. Indeed, our results show a statistically significant reduction in HRQOL for patients with a gastrostomy, dystonia, sialorrhea and needing a wheelchair. This could be a consequence of the physical limitations, stress and emotional impact of such clinical features. These could be addressed with priority when caring for these patients. Our results also show a reduced HRQOL in the presence of one or more of the nine clinical features investigated. This further supports the hypothesis that HRQOL is related to the severity of the clinical manifestations presented.

We elected to assess HRQOL in relation to the nine clinical variables mentioned above because they are common clinical features in this patient population. We had observed a trend between these variables and HRQOL in a preliminary analysis and existing literature in other patient populations suggests that some of these variables and the clinical severity of the disease may impact HRQOL. In cohorts of pediatric Cerebral Palsy patients, drooling was associated with a lower HRQOL[16]. In Mucopolysaccharidosis II, HRQOL scores were lower for patients with the severe form of

the disease compared to patients with the attenuated form[17]. In Mucopolysaccharidosis IVa, HRQOL was reduced in patients with high wheelchair reliance[18].

The highly compromised motor function as a result of the disease is reflected by the physical domain scores of the PedsQL 4.0 Generic Core Scales being the lowest, relative to the scores obtained for the emotional and social functioning domains. Our patient population frequently reported problems with running and walking more than one block, highlighting the physical limitations associated with genetically determined leukoencephalopathies. The utility of physical therapy and orthotic evaluation for this particular patient population has been suggested in the literature[19,20]. Our results highlight the importance of providing appropriate aids and adaptations to this patient population in order to help them achieve their maximal physical functioning potential and help them adapt to their physical limitations. When evaluating the benefits of specific interventions, it would be important to define the minimal clinically important difference in HRQOL necessary and the degree to which they improve HRQOL[21].

The lower social functioning score reported in the presence of specific clinical manifestations could possibly be a result of the cognitive and physical impairments, limiting their ability to take part in social activities. It is therefore important to take into account the social integration of these patients when designing their treatment plan. The PedsQL social functioning scores also include measures of physical disability (i.e. not being able to keep up with other children). However, this only accounts for a small percentage of the questions included and therefore the score obtained remains a good predictor of social functioning.

As for the emotional functioning domain, our study identified specific problems frequently encountered by this patient population. Trouble sleeping and worrying about what will happen to him/her were common emotions reported, reflecting the great emotional burden imposed by the incurable and, for the majority of them, degenerative nature of these diseases. Identification of these problems can help clinicians design specific interventions targeting these common issues.

Throughout our clinical encounters, we had the impression that having a precise molecular diagnosis helped patients and their families to better cope with the disease. However, our data showed a trend towards lower HRQOL in those with a precise molecular diagnosis. We believe that this is due to a more severe phenotype (i.e. greater disabilities) in patients with a molecular diagnosis versus no diagnosis in our specific patients' cohort. Indeed, patients with a molecular diagnosis accounted for 59% of patients with sialorrhea, 65% of patients needing a wheelchair and 67% of patients with dystonia. Although no statistically significant correlation was found between HRQOL and the presence/absence of a precise molecular diagnosis, we believe that this potential correlation should be further investigated with a larger patient cohort.

Concordance between the patients' and parents' perception of HRQOL was mainly strong except for the social and physical functioning domain where only a moderate agreement was noted. In those specific domains, parents perceived a poorer HRQOL as compared to the patient's assessment of his/her own HRQOL. This suggests that parents might not have a completely accurate view and understanding of the social and physical functioning of their affected child. This highlights the importance of considering the views of both, the affected child and the parents, when planning interventions and identifying the needs of these patients.

There are potential limitations to the present study. The reduced HRQOL seen in our study in the presence of certain clinical features could have been affected by several confounding factors that we did not control for such as socioeconomic and demographic factors. Controlling for these factors would have decreased the power of our analysis. Moreover, having analyzed the clinical features singularly, we did not investigate the role of interactions that could happen between them. A multivariate regression analysis would have better explained the results and was actually attempted at first. Unfortunately the degrees of freedom needed for this type of analysis using a single model were too high due to the low number of patients. Statistically significant lower scores were primarily found in the physical functioning domain, and very few were in the social/emotional functioning domains. However, we can still see a clear trend towards lower HRQOL scores within the social/emotional domains. A larger sample size could increase our chances of obtaining a statistically significant difference in those domains. As previously discussed, the response rate varied between scales/questionnaires potentially because some questions were found to be harder to answer by the participant possibly because the questionnaires were not disease-specific. As a consequence, the numbers of participants for some of the questionnaires are small limiting the conclusions that can be drawn from the study. A larger sample size would be required to increase the generalizability of our study results. Our patient population was unbalanced regarding the diagnoses because participants are recruited primarily from a subspecialized clinic for leukodystrophies with a specific expertise in 4H leukodystrophy. Since the clinical features and complications of LD and gLE are similar amongst the different disorders, we are confident that our results are applicable to the spectrum of disorders included in our study sample.

CONCLUSIONS

Genetically determined leukoencephalopathy patients are at risk for poor HRQOL. Our results show that HRQOL is influenced by the severity of clinical features presented by patients. By assessing HRQOL, we have identified areas of concern that can be targeted and prioritized when developing care strategies. Interventions should address these specific concerns regarding physical and social functioning. We have shown that using a wheelchair, having a gastrostomy, dystonia and sialorrhea are likely to impact HRQOL. Clinicians should pay particular attention to these features when deciding on supportive treatment strategies. For example, it is possible that prompt treatment of sialorrhea and maintenance of mobility for as long as possible may improve quality of life in this patient population. A multicenter prospective study enrolling a large number of patients is required to identify a larger inventory of modifiable factors.

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Table 1 : Total number of PedsQL 4.0 reports completed for genetically determined leukodystrophy patient sample

	Parent Proxy-Report *	Child Self-Report
	Number of reports completed (%)	
	N = 59	
PedsQL 4.0 Generic Core Scales **	n = 51 (86.4)	n = 16 (27.1)
Physical functioning		
Emotional functioning		
Social functioning		
School functioning		
Multidimensional Fatigue Scale **	n = 39 (66.1)	n = 15 (25.4)
General fatigue		
Sleep/rest fatigue		
Cognitive fatigue		

*Some parents did not fully complete the reports and therefore n ≠ 59 for the Parent Proxy-Reports.

**Parent Proxy-Reports available for age groups 1-12 months, 13-24 months, 2-4y, 5-7y, 8-12y, 13-18y, 18-25y and above 25y

Table 2 : Clinical Characteristics and Molecular Diagnosis for genetically determined leukoencephalopathy patient sample

	N = 59	Mean age (years : months)	SD
Male	38	8 : 10	6.91
Female	21	9 : 3	6.48
CLINICAL CHARACTERISTICS			
Sialorrhea	22	12 : 6	5.62
Wheelchair	26	12 : 0	5.49
Gastrostomy	9	6 : 10	6.10
Dystonia	33	11 : 1	7.30
Falls	19	10 : 1	5.96
Dysphagia	24	8 : 4	7.58
Seizures	16	6 : 2	4.59
Ataxia	27	12 : 0	7.20
Dysarthria	22	12 : 5	5.91
MOLECULAR DIAGNOSIS			
POLR3-related leukodystrophy	13	16 : 4	7.13
Aicardi-Goutieres syndrome	2	10 : 8	6.66
Cystic Leukoencephalopathy	1	8 : 4	0.00
X-Linked Adrenoleukodystrophy*	3	8 : 1	4.81
Sialic acid storage disease	2	13 : 6	3.54
Hypomyelination of the Early Myelinating Structures	1	10 : 11	0.00
Pelizaeus-Merzbacher-like disease	1	3 : 7	0.00
Pelizaeus-Merzbacher disease	2	13 : 10	4.84
Allan-Herndon-Dudley syndrome	3	8 : 7	4.38
Alexander Disease	3	10 : 0	4.95
CLCN2 Disease	1	15 : 0	0.00
Mucopolysaccharidosis type I	1	1 : 10	0.00
Hunter syndrome/ Mucopolysaccharidosis type II	1	2 : 11	0.00
San Filippo Type A/ Mucopolysaccharidosis type IIIA	1	4 : 8	0.00
1p36 deletion syndrome	1	1 : 1	0.00

Hypomyelination and Congenital cataract	1	4 : 3	0.00
Hypomyelination with atrophy of basal ganglia and cerebellum	1	3 : 7	0.00
No molecular diagnosis	21	5 : 10	4.24

*Two currently asymptomatic patients, one with Addison disease only

Table 3 : Comparison of PedsQL 4.0 Generic Core Scales and Multidimensional Fatigue Scale mean scores based on the presence or absence of certain clinical features

	Sialorrhea	No sialorrhea	Use of a wheelchair	No use of a wheelchair	Gastrostomy	No Gastrostomy	Dystonia	No dystonia
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
PedsQL 4.0 Generic Core Scales Parent Proxy-Report	*n = 20*	*n = 27*	*n = 21*	*n = 28*	*n = 7*	*n = 41*	*n = 25*	*n = 13*
Total Score	48.18* (20.12)	61.63* (18.90)	47.66* (18.83)	63.00* (19.48)	41.59* (21.54)	59.49* (19.33)	47.57* (19.40)	67.33* (14.80)
Physical functioning score	35.69* (29.09)	53.89* (29.72)	31.27* (28.48)	57.49* (28.68)	22.38* (32.64)	52.14* (28.41)	35.02* (27.49)	60.66* (32.04)
Emotional functioning score	57.92* (27.56)	71.86* (19.10)	62.36 (27.32)	71.97 (21.38)	56.43 (33.63)	68.82 (22.63)	61.98 (27.61)	74.42 (16.61)
Social functioning score	53.00 (22.44)	62.21 (25.54)	51.67 (20.15)	63.06 (26.79)	44.64 (14.47)	60.75 (25.23)	61.98 (27.61)	74.42 (16.61)
PedsQL 4.0 Generic Core Scales Child Self-Report	*n = 6*	*n = 9*	*n = 7*	*n = 9*	*n = 1*	*n = 13*	*n = 10*	*n = 5*
Total Score	51.66 (24.31)	74.71 (20.69)	53.29 (21.37)	71.93 (24.72)	36.25 (N/A)	69.77 (23.28)	51.38* (21.19)	84.35* (14.68)
Physical functioning score	32.74* (33.85)	70.83* (29.97)	28.95* (32.48)	70.83* (29.97)	9.38 (N/A)	62.47 (33.58)	34.02* (29.43)	83.75* (29.60)
Emotional functioning score	62.50 (16.66)	76.67 (27.95)	69.29 (12.05)	72.78 (30.53)	60.00 (N/A)	71.92 (26.18)	63.50 (24.61)	81.00 (15.97)
Social functioning score	59.17 (28.53)	79.07 (25.44)	65.71 (24.74)	72.96 (30.03)	45.00 (N/A)	75.13 (27.54)	58.17* (27.63)	93.00* (6.708)
School functioning score	65.42 (20.88)	74.17 (11.46)	65.36 (19.06)	71.39 (16.06)	62.50 (N/A)	73.27 (14.98)	61.00* (15.82)	80.00* (10.61)
Multidimensional Fatigue Scale Parent Proxy-Report	*n = 19*	*n = 17*	*n = 20*	*n = 17*	*n = 6*	*n = 30*	*n = 21*	*n = 9*

Comment [A1]: AUTHOR: Two different version of Table 3 and 5 captions has been provided in the separate file. Please confirm if the one that has been used is correct and amend if necessary.

Total Score	49.96* (23.36)	70.69* (19.88)	53.50 (24.18)	66.85 (21.83)	40.37* (22.76)	63.39* (22.47)	52.41* (21.41)	75.72* (18.73)
Multidimensional Fatigue Scale Child Self-Report	*n = 3*	*n = 10*	*n = 4*	*n = 11*	*n = 1*	*n = 13*	*n = 9*	*n = 4*
Total Score	62.96 (20.33)	68.93 (24.19)	58.68 (21.74)	65.44 (24.73)	44.44 (N/A)	67.13 (23.20)	48.46* (14.49)	84.03* (13.87)

*** P < .05**

Table 4 : HRQOL characterization in patients with genetically determined leukoencephalopathy and their families

A : HRQOL in relations to the number of clinical features presented by patients

	0/9 clinical features	>= 1/9 clinical features	P
	Mean (SD)	**Mean (SD)**	
PedsQL 4.0 Generic Core Scales Parent Proxy-Report	*n = 6*	*n = 44**	
Total Score	84.03 (9.845)	52.35 (18.40)	<0.001
Physical Functioning Score	87.38 (19.99)	40.73 (27.79)	<0.001
Emotional Functioning Score	89.38 (7.736)	64.45 (24.14)	<0.001
Social Functioning Score	80.83 (18.55)	54.24 (23.72)	0.01

B : Frequency of parents/ reporting "often" or almost always" for their child experiencing a specific problem on the PedsQL 4.0 Generic Core Scales Adults-Young Child Proxy-Reports domains

	Number of participants reporting the problem (%)	Specific problem
Physical Functioning	21 (67.7)	Difficulties with running
	20 (64.5)	Difficulties with walking more than 1 block
Emotional Functioning	5 (16.1)	Trouble sleeping
	5 (16.1)	Worrying what will happen to him/her
Social Functioning	23 (74.2)	Not keeping up with other adults/teens/children
	22 (71.0)	Not being able to do things that others his/her age can do

C : ICC between patient Self-Reports and Parent Proxy-Reports

	Parent-Child Agreement ICC
PedsQL 4.0 Generic Core Scales	
Total Score	0.780
Physical Functioning Score	0.431
Emotional Functioning Score	0.725
Social Functioning Score	0.491

Multidimensional Fatigue Scale	
Total Score	0.876

*An Emotional and Social Functioning score could not be obtained for one of the participants with >= 1/9 clinical features because these scales were not answered by the participant

Table 5 : Comparison of PedsQL 4.0 Generic Core Scales and Multidimensional Fatigue Scale mean scores based on the presence or absence of a precise molecular diagnosis

	Molecular diagnosis	No molecular diagnosis
	Mean (SD)	
PedsQL 4.0 Generic Core Scales Parent Proxy-Report	*n = 32*	*n = 18*
Total Score	53.33 (20.98)	61.16 (18.78)
Physical functioning score	43.73 (30.84)	50.93 (31.26)
Emotional functioning score	64.17 (26.16)	73.24 (18.58)
Social functioning score	54.19 (25.00)	63.19 (54.19)
PedsQL 4.0 Generic Core Scales Child Self-Report	*n = 14*	*n = 2*
Total Score	62.25 (25.37)	74.45 (19.21)
Physical functioning score	50.86 (37.17)	64.06 (46.4)
Emotional functioning score	71.07 (24.90)	72.50 (17.68)
Social functioning score	67.26* (28.24)	87.5* (3.54)
School functioning score	67.14* (17.76)	80.00* (0.00)
Multidimensional Fatigue Scale Parent Proxy-Report	*n = 25*	*n = 13*
Total Score	55.35 (25.47)	66.92 (17.81)
Multidimensional Fatigue Scale Child Self-Report	*n = 13*	*n = 2*
Total Score	60.18 (23.27)	86.11 (1.96)

* P < .05