Systematic review of functional assessment scales in Pompe disease

Revisão sistemática das escalas utilizadas para avaliação funcional na doença de Pompe

Revisión sistemática de las escalas utilizadas para evaluación funcional en la enfermedad de Pompe

Alana Karla Savegnago[1], Rosângela Maria da Silva[2], Cíntia Jonhston[3], Ana Maria Martins[4], Ana Paula L. de Melo[5], Werther Brunow de Carvalho[6]

ABSTRACT

Objective: To identify functional assessment scales used in Pompe disease (PD) and to describe their levels of evidence and grades of recommendation.

Data source: Systematic review of the functional assessment scales used in PD. Review conducted in the databases Medline, Lilacs, Cochrane Central Register of Controlled Trials (CCTR), and SciELO including articles (except review articles) published between 2000 and 2010. The key-words used in Portuguese and English were: glycogen storage disease type II, activities of daily living, assessment. The articles were classified according to their level of evidence and grade of recommendations.

Data synthesis: 14 studies assessing patients ranging from newborns to adults were included in the present review (total sample=449). The scales found in the literature were: Pediatric Evaluation of Disability Inventory (PEDI) and its adapted version for PD (Pompe-PEDI), Alberta Infant Motor Scale (AIMS), Rotterdam Handicap Scale (RHS), Functional Independence Measure (FIM), Gross Motor Function Measure (GMFM), and Peabody Developmental Motor Scales (PDMS-II). Most studies had level of evidence III because they were non-randomized studies. The grades of recommendation of the scales were C for AIMS and Pompe-PEDI, D for GMFM and PDMS-II; and E for RHS and FIM.

Conclusions: Most functional assessment scales used in PD show low level of evidence and grade of recommendation. The scales showing the highest grade of recommendation (C) were the AIMS and Pompe-PEDI used in Pediatrics.

Key-words: glycogen storage disease type II; activities of daily living; evaluation.

RESUMO

Objetivo: Identificar as escalas utilizadas para avaliação funcional na doença de Pompe (DP) e descrever seu nível de evidência e recomendação.

Fontes de dados: Revisão sistemática sobre as escalas de avaliação funcional na DP. Pesquisa realizada nos bancos de dados Medline, Lilacs, Registro Cochrane de Ensaios Controlados Central (CCTR) e SciELO com artigos (exceto artigos de revisão) publicados entre 2000 e 2010. As palavras-chave utilizadas nos idiomas português e inglês

Instituição: Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brasil

[1]Aperfeiçoanda em Fisioterapia Pediátrica em Cuidados Intensivos e Semi-intensivos da Escola Paulista de Medicina da Unifesp, São Paulo, SP, Brasil

[2]Mestranda em Pediatria pela Escola Paulista de Medicina da Unifesp; Fisioterapeuta do Hospital São Paulo/SPDM e do Centro de Referência em Erros Inatos do Metabolismo, São Paulo, SP, Brasil

[3]Pós-doutoranda em Pneumologia pela Escola Paulista de Medicina da Unifesp; Coordenadora dos Cursos de Especialização em Fisioterapia Pediátrica e Neonatal da Escola Paulista de Medicina da Unifesp, São Paulo, SP, Brasil

[4]Pós-doutora em Dismorfologia pela *University of California*, Estados Unidos; Diretora do Centro de Referência em Erros Inatos do Metabolismo e Professora Adjunta do Departamento de Pediatria da Escola Paulista de Medicina da Unifesp, São Paulo, SP, Brasil

[5]Mestranda em Ciências da Saúde pela Escola Paulista de Medicina da Unifesp; Vice-coordenadora do Serviço de Fisioterapia Pediátrica e Neonatal do Hospital São Paulo/SPDM, São Paulo, SP, Brasil

[6]Doutor em Pediatria e Ciências Aplicadas à Pediatria pela Escola Paulista de Medicina da Unifesp; Professor Titular em Terapia Intensiva/Neonatologia da Universidade de São Paulo (USP), São Paulo, SP, Brasil

Endereço para correspondência:
Ana Maria Martins
Rua Coronel Lisboa, 957 – Vila Clementino
CEP 04020-041 – São Paulo/SP
E-mail: ana.martins@unifesp.br

Fonte financiadora: Actelion, Biomarim, Genyme e Shire – auxílio para participação em congressos
Conflito de interesse: nada a declarar

Recebido em: 5/5/2011
Aprovado em: 17/10/2011

foram: doença de depósito de glicogênio tipo II, atividades cotidianas, avaliação. Os artigos foram classificados em nível de evidência e recomendação.

Síntese dos dados: Foram incluídos 14 estudos que avaliaram desde recém-nascidos a adultos (amostra total=449). Foram encontradas as seguintes escalas na literatura: *Pediatric Evaluation of Disability Inventory* (PEDI) e sua forma adaptada para DP (Pompe-PEDI), *Alberta Infant Motor Scale* (AIMS), *Rotterdam Handiscap Scale* (RHS), *Functional Independence Measure* (FIM), *Gross Motor Function Measure* (GMFM) e *Peabody Developmental Motor Scales* (PDMS-II). A maioria dos estudos apresentou nível de evidência III, por serem não randomizados. Grau de recomendação das escalas: C para AIMS e Pompe-PEDI; D para GMFM e PDMS-II; E para RHS e FIM.

Conclusões: A maioria das escalas utilizadas para avaliação funcional na DP apresenta baixo nível de evidência e recomendação. As que apresentam melhor grau de recomendação (C) são as escalas AIMS e Pompe-PEDI aplicadas em Pediatria.

Palavras-chave: doença de depósito de glicogênio tipo II; atividades cotidianas; avaliação.

RESUMEN

Objetivo: Identificar las escalas utilizadas para evaluación funcional en la enfermedad de Pompe (EP) y describir su nivel de evidencia y recomendación.

Fuentes de datos: Revisión sistemática sobre las escalas de evaluación funcional en la EP. Investigaciones realizadas en las bases de datos Medline, Lilacs, Registro Cochrane de Ensayos Controlados Central (CCTR) y SciELO con artículos (excepto artículos de revisión) publicados entre 2000 y 2010. Las palabras clave utilizadas en los idiomas portugués e inglés fueron: enfermedad de depósito de glucógeno tipo II, actividades cotidianas, evaluación. Los artículos fueron clasificados en nivel de evidencia y recomendación según Cook *et al*.

Síntesis de los datos: Se incluyeron 14 estudios que evaluaron desde recién-nacidos a adultos (muestra total=449). Se encontraron las siguientes escalas en la literatura: *Pediatric Evaluation of Disability Inventory* (PEDI) y su forma adaptada para 1DP (Pompe-PEDI), *Alberta Infant Motor Scale* (AIMS), *Rotterdam Handiscap Scale* (RHS), *Functional Independence Measure* (FIM), *Gross Motor Function Measure* (GMFM) y *Peabody Developmental Motor Scales* (PDMS-II). La mayoría de los estudios presentó nivel de evidencia III, por tratarse de estudios no randomizados. Grado de recomendación de las escalas: C para AIMS y Pompe-PEDI; D para GMFM y PDMS-II; E para RHS y FIM.

Conclusiones: La mayoría de las escalas utilizadas para evaluación funcional en la EP presenta bajo nivel de evidencia y recomendación. Las que presentan mejor grado de recomendación (C) son las escalas AIMS y Pompe-PEDI aplicadas en Pediatría.

Palabras clave: enfermedad de depósito de glucógeno tipo II; actividades cotidianas; evaluación.

Introduction

Pompe disease (PD), also known as glycogen storage disease type II, is an autosomal recessive inheritance disease, caused by the deficiency of the acid alpha-glucosidase (GAA) enzyme responsible for degradation of lysosomal glycogen. This enzyme deficiency results in lysosomal glycogen accumulation in different tissues, with skeletal, cardiac and smooth muscle most prominently involved[1,2].

The infantile form (infantile-onset Pompe disease) affects children in the first months of life, with the following clinical manifestations: cardiomyopathy (dilated or hypertrophic), hypotonia and muscle weakness of rapid progression. In general, the child evolves to death due to cardiorespiratory failure in the first year of life.

The late-onset disease (late-onset Pompe disease) can manifest at any age between the 1st year until the 6th decade of life. Typically, this late form of the disease does not include severe cardiomyopathy and is characterized by presenting a slower disease progression than the infantile form. Muscle weakness is the main symptom, predominantly in the proximal muscles with an extensive involvement of the lower limbs, resulting in loss of motor function and difficulty in performing daily living activities. With disease progression, patients become wheelchair users and may become dependent on mechanical ventilation due to respiratory failure, which is the main cause of morbidity and mortality[2,3].

Musculoskeletal involvement is characterized by a progressive replacement of the contractile tissue by a fibrotic inactive tissue, causing progressive loss of muscular strength with motor function impairment, postural changes and the use of compensatory patterns of movement. Secondary musculoskeletal impairments include contractures and deformities that compromise the function[3,4]. The extent

and the distribution of muscle weakness depend on the severity of the disease. It often involves all members and is symmetrical, being greater in the proximal muscles and lower limbs[1,4].

Currently, the treatment of PD is made by enzyme replacement therapy (ERT) with the recombinant human alpha-glucosidase enzyme, approved in 2006 by the European Medicines Agency and the Food and Drug Administration[3,4]. The ERT has provided significant improvement in cardiac and skeletal muscle function, prolonging survival and reducing mortality[4]. However, this therapeutic option inflicts the use of specific and validated assessment methods, so as to report changes in parameters related to disease progression and therapeutic response. To monitor the progression of the PD and to guide the necessary treatments/interventions, clinical and functional assessments are recommended in short periods of time, every three to six months in both clinical presentations of the disease[3].

The functional assessment scales for patients with PD are poorly known in the medical field. This disease requires specific assessment methods to identify and monitor early functional changes, as well as to outline appropriate methods of prevention and treatment for this population. This way, this systematic review aimed to identify the functional assessment scales that can be used in these cases and their level of evidence and recommendation.

Method

We performed a systematic review about functional assessment scales in children and adults with PD.

The inclusion criteria used in selecting articles for the review were the study design (randomized clinical trials, cohort, case-control, cross-sectional, case reports and case series), the language (Portuguese, English) and the use of functional scales used to assess function and functional independence of the pediatric and adult population with PD, with or without ventilator and mobility devices (e.g. wheelchairs) dependence and, with or without enzyme replacement therapy. Studies that were focused only on the PD, without the use of functional assessment scales or those who used them in other genetic diseases related to inborn errors of metabolism were excluded.

For the research a manual electronic search was performed on Medline, Lilacs Cochrane Central Register of Controlled Trials (CCTR) and SciELO with articles (except for review articles) published between 2000 and 2010. The key-words used in Portuguese and English, respectively, were: *doença de depósito de glicogênio tipo II, atividades cotidianas, avaliação*, glycogen storage disease type II, activities of daily living, assessment.

The selected articles were classified in level of evidence (from I to V, being I the greatest level of evidence) and recommendation (from A to E, being A the greatest level of recommendation) according to Cook *et al*[5] (Chart 1). The analysis of the quality of the articles was performed by two independent evaluators who agreed in their classification.

Results

We found 25 studies, of which 14 met the inclusion criteria for this systematic review. These articles assessed from newborn to adults, with a total sample of 449 individuals.

Chart 1 - The grading of recommendations and the levels of evidence for scientific articles, according to Cook *et al*[5]

Grades of Recommendation	
A	Supported by, at least, two level I investigations
B	Supported only by one level I investigation
C	Supported only by level II investigations
D	Supported by, at least, one level III investigation
E	Supported by level IV or V Evidence
Evidence Levels	
Level I	Randomized trials; great sample size; clear results; low risk of alpha (false-positive) or beta (false-negative) errors
Level II	Randomized trials; small sample size; uncertain results; moderate to high risk of alpha (false-positive) or beta (false-negative) errors
Level III	Nonrandomized, contemporaneous controls
Level IV	Nonrandomized, historical control and experts opinion
Level V	Case series; without control subjects and experts opinion

The 11 remaining studies were excluded because they did not address functional assessment scales.

The scales found in literature for functional assessment in the population with PD were: five studies with the Pediatric Evaluation of Disability Inventory (PEDI) scale and its adapted form for PD (Pompe-PEDI); seven studies with Alberta Infant Motor Scale (AIMS); two studies with Rotterdam Handicap Scale (RHS); one study with the Functional Independence Measure (FIM); two studies with the Gross Motor Function Measure (GMFM) and one with the Peabody Developmental Motor Scales (PDMS-II). Five studies used more than one scale for functional assessment. The Pompe-PEDI scale is the only one specific and validated for this disease[6].

Most studies presented level III evidence because they were nonrandomized studies. Scales grades of recommendation: C for AIMS and Pompe-PEDI; D for GMFM and PDMS-II; E for RHS and FIM. Table 1 presents the articles found, the classification of the level of scientific evidence and the scales of functional assessment used.

Discussion

The purpose of the functional assessment scales is to evaluate and monitor the functional performance, as well as to assist in developing methods for prevention and treatment for children and adults with some degree of physical disability[7]. This systematic review identified the scales used for functional assessment of children and adults with PD described in literature. It was observed that, so far, six scales[6-19] were used, and only the Pompe-PEDI scale is specific and validated for this population[1-3].

We found five studies that used PEDI scale and its adapted form for Pompe. PEDI is an instrument of broad functional assessment that measures the capacity and the performance of functional activities, including self-care and mobility. It was designed primarily to evaluate children. It can be applied to assess adolescents, if their functional abilities are below the expected for a 7-year-old child without disabilities. In these studies, it was used to assess individuals from 4 months old to 32 years old[6,8].

Haley *et al*[6] made a study to adapt the PEDI scale for individuals with deficiency of the GAA enzyme. The authors modified the original scale and included 77 items of mobility and 19 items about self-care, which reflect the abilities and disabilities present in PD. Parents from 30 children and young people (mean age 7.7±5.6 years) were interviewed by telephone. The score obtained on the Pompe-PEDI scale was compared to the PEDI original scale and the reliability test was performed with parents of six children, and the interclass correlation coefficient (ICC) was 0.99 to self-care abilities and 0.98 for mobility skills. The Pompe-PEDI scale validity was determined by comparing the score of the Gross Motor Function Classification System (GMFCS), which is a standardized system with five levels, representing the degrees of limitation of gross motor function. The authors demonstrated the validity of the Pompe-PEDI scale to discriminate differences in motor function, when compared with the GMFCS. As a result of

Table 1 - Classification of the studies that used scales for functional assessment of the Pompe disease

	Design	Sample	Scale
Haley *et al*[6]	Level III	30 children and adolescents from 0.5–22.1* years	PEDI
Haley, Fragala e Skrinar[7]	Level III	30 children and adolescents from 0.5–22.1* years	Pompe-PEDI
Haley *et al*[8]	Level IV	26 children from 0.4-14* years	Pompe-PEDI
Winkel *et al*[9]	Level III	2 children and 1 adult from 11-32* years	PEDI GMFM
Kishnani *et al*[10]	Level II	18 children from 4.6±1.7** months	Pompe-PEDI AIMS
Kishnani *et al*[11]	Level II	18 children from 4.6±1.7** months	AIMS
Klinge *et al*[12]	Level III	2 children from 3.1 and 5.9 months	AIMS
Klinge *et al*[13]	Level III	2 children from 14.0 and 16.8 months	AIMS
Van den Hout *et al*[14]	Level III	4 children from 2.5–8.0* months	AIMS
But *et al*[15]	Level V	1 child of 5.5 months	AIMS
Chien *et al*[16]	Level III	6 children from 7–40* days	AIMS PDMS-II
Hagemans *et al*[17]	Level IV	257 adults from 48±13** years	RHS
Hagemans *et al*[18]	Level IV	52 adults from 48±16** years	RHS
Case *et al*[19]	Level V	1 adult of 63 years	GMFM FIM

PEDI: Pediatric Evaluation of Disability Inventory; GMFM: Gross Motor Function Measure; AIMS: Alberta Infant Motor Scale; PDMS-II: Peabody Developmental Motor Scale; RHS: Rotterdam Handicap Scale; FIM: Functional Independence Measure; *age in minimum-maximum; **age in mean±standard deviation

the study, Pompe-PEDI scale proved to be a valid instrument to assess and monitor functional changes in children and young people with PD.

In another study, Haley, Fragala e Skrinar[7] assessed the degree of physical disability of these children and adolescents through the application of the Pompe-PEDI scale by telephone interviews. To estimate the functional delay, authors used the original PEDI scale to calculate the age-appropriate score in the categories mobility and self-care. The two scales, original and adapted, served as a basis to create a computer-adapted test to reduce the evaluation time[8]. In this study, authors evaluated the score obtained in the functional assessment of children from 4 months old to 14 years from two previous studies[7,8]: 26 children with com PD in which the Pompe-PEDI scale was used and 373 children with other diseases, who participated in the study of development and standardization of the PEDI scale.

Two other studies[9,10] used the PEDI and Pompe-PEDI scales to assess the effects of replacement therapy with recombinant GAA in motor function. The first is a pilot follow-up study[9] that assessed three individuals with late-onset PD (aged 11, 16 and 32 years), in which the GMFM scale was also applied to assess the gross motor skills. The second is a randomized controlled multicenter study[10] that applied the Pompe-PEDI scale with the AIMS in 18 children (mean age of 4.6±1.7 months) seriously affected by the classical infantile form of PD.

The AIMS is an instrument used to assess motor skills acquired from birth to 18 months old. In a study[11] extending the work of Kishnani *et al*[10], in which the effects of long-term continuous treatment with the recombinant GAA in the same sample of 18 children were described, the AIMS was used until the patient reached the maximum score on this scale. The age of the last functional evaluation ranged from 16 to 37.6 months, most being above the standardized age.

Some studies[12-15] applied the AIMS to assess the effects of enzyme replacement therapy. Chien *et al*[16], in 2009, followed six infants (aged 7 to 40 days of life) of a pilot program of neonatal screening during 14 to 33 months of treatment and applied two assessment scales, AIMS and PDMS-II. The first identified motor developmental delay in the sample and the second, greater delay in the gross motor function than in the fine. A PDMS-II is an assessment scale of the fine and gross motor development for infants and children (from 6 months to 6 years of age), consisting of four subtests of gross motor function and two of fine motor function.

The Rotterdam Handicap Scale is a short scale that assesses the level of independence in the daily activities of patients with neuromuscular disorders, used in two studies[17,18]. The cross-sectional follow-up study[18] applied a questionnaire to a sample of 52 individuals aged above 18 years (mean 48±16 years) after 1 and 2 years of the beginning of the research project. Another prospective cross-sectional study[17] evaluated the applicability of the RHS in individuals with PD. We also analyzed the responses in a questionnaire in a sample of 257 individuals aged above 18 years (mean of 48±13 years). Reliability test was used with a subgroup of 29 individuals who completed the RHS twice in the interval of approximately one month (ICC=0.94), recommending its use in PD.

In a case report[19] of a 63-year-old woman affected by the late-onset Pompe disease, who received enzyme replacement therapy for 2 years, her functional evaluation was performed by the GMFM and FIM scales. The latter is widely used in various diseases that cause functional alterations and evaluates the overall performance in activities of daily living, assessing both motor and cognitive functions.

In the pediatric population, the scales were more frequently applied were the AIMS, particularly in infants, and the PEDI and Pompe-PEDI scales in older children and young people with functional capacity lower than expected for a 7-year-old child. In adult patients, the RHS was the most commonly used scale.

The functional assessment scales in PD were used primarily to assess the effects of enzyme replacement therapies. However, they can also be indicated to evaluate the functional performance before and after the institution of rehabilitation programs.

Conclusion

Most scales used for PD functional assessment present a low level of evidence and recommendation. Those with the best grade of recommendation (C) are the AIMS and Pompe-PEDI scales, applied to Pediatrics.

Only the Pompe-PEDI scale is specific for the functional assessment of PD. Only the Rotterdam Handicap Scale had its applicability assessed in patients with this disease, however, it is limited for use in individuals aged over 18 years.

References

1. Kishnani PS, Steiner RD, Bali D, Berger K, Byrne BJ, Case LE *et al*. Pompe disease diagnosis and management guideline. Genet Med 2006;8:267-88.
2. Kishnani PS, Howell RR. Pompe disease in infants and children. J Pediatr 2004;144 (Suppl 5):S35-43.
3. Llerena JC Jr, Horovitz DM, Marie SK, Porta G, Giugliani R, Rojas MV *et al*. The Brazilian consensus on the management of Pompe disease. J Pediatr 2009; 155 (Suppl 4):S47-56.
4. Bembi B, Cerini E, Danesino C, Donati MA, Gasperini S, Morandi L *et al*. Management and treatment of glycogenosis type II. Neurology 2008;71 (23 Suppl 2):S12-36.
5. Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotics agents. Chest 1992;102 (4 Suppl):305S-11.
6. Haley SM, Fragala MA, Aseltine R, Ni P, Skrinar AM. Development of a disease-specific disability instrument for Pompe disease. Pediatr Rehabil 2003;6:77-84.
7. Haley SM, Fragala MA, Skrinar AM. Pompe disease and physical disability. Dev Med Child Neurol 2003;45:618-23.
8. Haley SM, Ni P, Fragala-Pinkham MA, Skrinar AM, Corzo D. A computer adaptive testing approach for assessing physical functioning in children and adolescents. Dev Med Child Neurol 2005;47:113-20.
9. Winkel LP, Van den Hout JM, Kamphoven JH, Disseldorp JA, Remmerswaal M, Arts WF *et al*. Enzyme replacement therapy in late-onset Pompe's disease: a three-year follow-up. Ann Neurol 2004;55:495-502.
10. Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, Hwu WL *et al*. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology 2007;68:99-109.
11. Kishnani PS, Corzo D, Leslie ND, Gruskin D, Van der Ploeg A, Clancy JP *et al*. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. Pediatr Res 2009;66:329-35.
12. Klinge L, Straub V, Neudorf U, Schaper J, Bosbach T, GörlingerK *et al*. Safety and efficacy of recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease: results of a phase II clinical trial. Neuromuscul Disord 2005;15:24-31.
13. Klinge L, Straub V, Neudorf U, Voit T. Enzyme replacement therapy in classical infantile pompe disease: results of a ten-month follow-up study. Neuropediatrics 2005;36:6-11.
14. Van den Hout JM, Kamphoven JH, Winkel LP, Arts WF, De Klerk JB, Loonen MC *et al*. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. Pediatrics 2004;113:e448-57.
15. But WM, Lee SH, Chan AO, Lau GT. Enzyme replacement therapy for infantile Pompe disease during the critical period and identification of a novel mutation. Hong Kong Med J 2009;15:474-7.
16. Chien YH, Lee NC, Thurberg BL, Chiang SC, Zhang XK, Keutzer J, *et al*. Pompe disease in infants: Improving the prognosis by newborn screening and early treatment. Pediatrics 2009;124:e1116-25.
17. Hagemans ML, Laforêt P, Hop WJ, Merkies IS, Van Doorn PA, Reuser AJ *et al*. Impact of late-onset Pompe disease on participation in daily life activities: evaluation of the Rotterdam Handicap Scale. Neuromuscul Disord 2007;17:537-43.
18. Hagemans ML, Hop WJ, Van Doorn PA, Reuser AJ, Van der Ploeg AT. Course of disability and respiratory function in untreated late-onset Pompe disease. Neurology 2006;66(4):581-3.
19. Case LE, Koeberl DD, Young SP, Bali D, DeArmey SM, Mackey J *et al*. Improvement with ongoing enzyme replacement therapy in advanced late-onset Pompe disease: a case study. Mol Genet Metab 2008;95:233-5.