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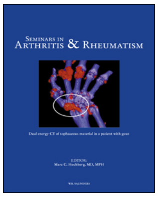

Fatigue in patients with juvenile idiopathic arthritis: A systematic review of the literature

Wineke Armbrust, MD[a,*], Nicole E. Siers, MSc[b], Otto T.H.M. Lelieveld, PhD[c], Leonora J. Mouton, PhD[b], Jolanda Tuinstra, PhD[d], Pieter Sauer, PhD[e]

[a] *Department of Pediatric Rheumatology, Beatrix Children's Hospital, University Medical Center Groningen (UMCG), University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands*
[b] *Center for Human Movement Sciences, University Medical Center Groningen (UMCG), University of Groningen, A. Deusinglaan 1, Groningen, The Netherlands*
[c] *Center for Rehabilitation, University Medical Center Groningen (UMCG), University of Groningen, Hanzeplein 1, Groningen, The Netherlands*
[d] *Department of Health Sciences, University Medical Center Groningen (UMCG), University of Groningen, Oostersingel, entrance 45, Groningen, The Netherlands*
[e] *Department of Pediatric Rheumatology, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen (UMCG), Hanzeplein 1, Groningen, The Netherlands*

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ABSTRACT

Objective: To perform a systematic review of the current literature on studies related to fatigue in children with JIA. We studied the measurements that were used to assess fatigue and we focused on three outcome measurements, namely, (1) the prevalence of fatigue in JIA patients, (2) the determinants of and associations with fatigue in JIA patients, and (3) the impact of fatigue in JIA patients on daily life.
Methods: A search was conducted in the electronic databases Pubmed and Embase from January 1, 2000 until August 27, 2015. The quality in prognostic factors (QUIPS) tool was used to assess the risk of bias (ROB) in the selected studies, focused on the outcome fatigue. Of all, two authors independently judged the ROB.
Results: A total of 15 studies were included in this review. To assess fatigue, two unidimensional and three multidimensional scales were used, which hampered comparison. Fatigue was reported to be present in 60–76% of the patients with JIA and was related to time of day, disease activity, pain, psychosocial factors, and sleep. Minor consequences for daily life were found, though this was not studied extensively.
Conclusion: Fatigue is common in patients with JIA. The cause reflects a complex interplay of different factors. Based on results from this review and its body of knowledge, a conceptual model for fatigue in patients with JIA is proposed. Consensus is needed for future studies on how to assess fatigue. We promote the use of a combination of unidimensional and validated multidimensional measurements.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood, affecting at least 0.2 per 1000 children [1]. Although the treatment has improved, disease flares are still common [2]. Regardless of the fluctuations in disease activity, children with JIA suffer from daily symptoms such as pain, stiffness, and fatigue [3,4]. However, fatigue is often seen as a side effect of treatment, or as a sign or symptom of JIA; it is essentially a subjective experience, whose cause still remains unknown. It is likely associated with clinical variables and psychosocial variables [4–7]. The consequences of fatigue can be major, as they hamper children's performance at school, social life, sports, and hobbies [8].

At present, no good overview of fatigue in JIA exists, either in terms of its prevalence or its determinants, or on the impact it has on daily life. Including measurements of fatigue in disease monitoring by patient reported outcome measures (PROMs) [9] could be a way to learn more about these issues. However, in that case, consensus is needed as to how to measure fatigue in patients with JIA. Such a consensus does not exist; this is related to the lack of a uniform definition that, in turn, hampers the different possible aspects of fatigue in JIA that can be studied.

In chronic disease, fatigue is often referred to as a "persistent, overwhelming sense of tiredness, weakness or exhaustion, resulting in a decreased capacity for physical and/or mental work and is unrelieved by sleep or rest" [10,11]. In this definition, the impact is included and the cause of the fatigue remains undefined.

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[*] Corresponding author.
E-mail address: w.armbrust@umcg.nl (W. Armbrust).

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Fatigue is multidimensional in its manifestation and its impact. The manifestation of fatigue can be physical and mental. Physical fatigue refers to a feeling of tiredness such as feeling weak, whereas mental fatigue covers the cognitive symptoms of fatigue such as problems with concentration [12,13]. The impact of fatigue effects the physical, personal, and psychosocial domains [14]. To study the cause and the impact of fatigue in patients with JIA, it is of great importance to approach this subject in a multidimensional way. For these reason multidimensional measurements that assess physical, cognitive, and psychosocial dimensions of fatigue seem preferable to unidimensional measurements such as the visual analogue scale (VAS) that measures the intensity or frequency of fatigue.

The aim of this study was to perform a systematic review of the current literature on studies related to fatigue in children with JIA. We studied the measurements that were used to assess fatigue and we focused on three outcome measurements, namely, (1) the prevalence of fatigue in JIA patients, (2) the determinants of and associations with fatigue in JIA patients, and (3) the impact of fatigue in JIA patients on daily life.

Methods

We used the preferred reporting item for systematic reviews and meta-analyses (PRISMA) for the critical appraisal of the literature and reporting in this review [15].

Search method

Of all, two authors (W.A. and N.S.) performed a search in the electronic databases Pubmed and Embase from January 1, 2000 until August 27, 2015, using the algorithm as described in Table 1.

Inclusion and exclusion of studies

Of all, two authors (W.A. and N.S.) screened all titles and abstracts for applicability to the research subject, using predefined inclusion criteria such as patient-reported outcome studies concerning fatigue for all ages and all types of JIA; and juvenile chronic arthritis (JCA) or juvenile rheumatoid arthritis (JRA), according to the International League Against Rheumatism (ILAR), the European League Against Rheumatism (EULAR), and the American College of Rheumatology (ACR). At least one of the three outcome parameters, as described in the aim of this study, had to be studied, and fatigue had to be a primary or secondary outcome parameter as described in the methods. Articles had to be in English. Patients of all ages were included.

Exclusion criteria were articles that presented results on fatigue in chronic (autoimmune) diseases, without presenting, and discussing the results of JIA patients separately.

Table 1
Terms used and results in searching for fatigue in patients with JIA in Pubmed and Embase

		Pubmed	Embase
1	(“Arthritis, Juvenile”[Mesh] OR juvenile arthritis[tw] OR juvenile polyarthritis[tw] OR juvenile oligoarthritis [tw] OR jia[tw] OR jca[tw] OR jra[tw])	9634	16,494
2	(“Fatigue”[Mesh] OR fatigue*[tw] OR tired*[tw])	75,025	165,393
3	1 AND 2	58	289

Mesh = mesh term, tw = title word.

Methodological assessment

The quality in prognostic factors (QUIPS) tool was used to assess the risk of bias (ROB) in the studies selected for their focus on the outcome fatigue [16]. The QUIPS tool is an easy tool for assessing the risk of bias in outcome measurements, in our case fatigue. The median inter-rater agreement was 0.75 in 43 studies investigating prognostic factors of different outcome parameters (16). With the QUIPS tool, six domains were judged, namely, study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. We added an item to judge the ROB for perceived impact of fatigue. Each domain consisted of 3–7 sub-items, for example, the domain study participation consisted of the items adequate participation of eligible persons, description of source population, description of baseline population, description of place and time of recruitment, and adequate description of inclusion and exclusion criteria. A complete set of domains and items are described in Appendix A. Each item was rated as high, moderate, or low bias, resulting in a score for the whole domain as described in Appendix B. An article was excluded when high bias was scored on 3 or more domains, or if the article did not report the prevalence or incidence of fatigue, or if the article did not report prognostic factors or impact.

Of all, two authors (W.A. and N.S.) judged the ROB, and a Cohen's correlation coefficient for the agreement was calculated. In case of disagreement, the results were discussed, and an expert was consulted.

Synthesis

Results are reported in a descriptive way. Meta-analysis was not applicable due to the heterogeneity of the studies. *General characteristics* of the studies were reported as follows: author, country of the performed study, study design, control group yes or no, period of inclusion, number of included patients, and proportion of males, age, and disease duration. *Outcome measurements* were aim of the study, values reported on the fatigue scales, frequency of fatigue, significant outcome, and reported conclusions regarding fatigue. The reported results were clustered by the dimensionality of the measurements to assess fatigue: unidimensional on severity or intensity, and multidimensional, which also included separate physical, cognitive, and psychosocial dimensions.

Results

Methodological assessment

The search resulted in 382 articles, of which 21 were submitted for a methodological assessment (Fig. 1). The methodological assessment of the ROB can be found in Appendix B. The Cohen's correlation coefficient was 0.8 for the authors. Reasons for moderate or high ROB are provided (Appendix B). Overall 6 of the 21 articles were excluded for this review: four because of high ROB [17–20], and two articles because none of the outcome parameters were reported [21,22]. A final set of 15 articles was included for this review, comprising 11 separate studies. overall, four pairs of articles published (in part) concerning the same study population. Minden et al. [23] and Raab et al. [24] both reported about an ongoing prospective cohort of patients receiving Etanercept in Germany. Ostlie et al. [25,26] published two articles on the same cohort: one article presented the results of a longitudinal study on physical and psychosocial health in JIA patients, and in the other JIA outcomes were compared to population norms. Stinson et al. [27,28] also published two articles on the same population: one