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CLINICAL REVIEW

A systematic review of cognitive function and psychosocial well-being in school-age children with narcolepsy

Jane E. Blackwell, Hetaf A. Alammar, Anna R. Weighall*, Ian Kellar, Hannah M. Nash

School of Psychology, University of Leeds, Leeds, LS2 9JT, UK

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SUMMARY

In August 2010, concerns were raised about an increase in the incidence rate of narcolepsy diagnosis in children and adolescents. Narcolepsy is a chronic neurological sleep disorder characterised by excessive daytime sleepiness and attacks of muscle weakness which are often precipitated by strong emotions, known as cataplexy. We systematically examined and updated the scientific literature on the consequences of narcolepsy on cognitive function and psychosocial well-being in school-age children. Eight studies published between 2005 and 2015 were eligible for inclusion in this review. Collectively the results provide evidence to suggest that children who develop narcolepsy are at significant risk of cognitive impairment in at least one domain and emotional problems including depression, anxiety and low self-esteem. Children with narcolepsy should be monitored carefully in order to manage and reduce the impact of any impairments present. The existing literature is limited by small sample sizes, lack of appropriate controls and lack of longitudinal data. Future research should aim to address the limitations of the current work and aim to determine the underlying cause of cognitive and psychological impairments. This will enable the design of effective interventions to support children with narcolepsy so that they are able to achieve their full potential.

Introduction

Narcolepsy is a chronic and disabling neurological sleep disorder characterised by excessive daytime sleepiness (EDS) and attacks of muscle weakness which are often precipitated by strong emotions (cataplexy). The estimated prevalence of narcolepsy with cataplexy in western countries is 25–50 per 100,000 [1]. The International classification of sleep disorders-third edition (ICSD-3, 2014) [2] distinguishes between two types of narcolepsy; narcolepsy type 1 and narcolepsy type 2. Individuals with type 1 narcolepsy experience cataplexy or have a deficiency of the neuropeptide hypocretin, whereas individuals with type 2 narcolepsy do not experience cataplexy and the relationship to cerebrospinal levels of hypocretin is less definite.

Narcolepsy is a condition that has traditionally been thought of as a disease of adulthood [3] however, contrary to this assumption, more than 50% of individuals with narcolepsy report experiencing the onset of symptoms before the age of 18 y [4], typically during adolescence. Children and adolescents with narcolepsy are at increased risk of their condition being unrecognised, misinterpreted and misdiagnosed due to the disorder's wide range of clinical manifestations [5]. EDS is the most commonly reported first symptom of narcolepsy and therefore it can be difficult for the clinician to distinguish between the normal requirement for daytime naps during childhood and excessive need for sleep. Cataplexy, which is a unique and characteristic feature of narcolepsy, may only appear many years after the development of EDS. It has been estimated that delays between the onset of symptoms and the diagnosis of narcolepsy can range from 10 to 15 y [6]. Individuals with narcolepsy display a great deal of variation in their presentation and this can lead to misinterpretations of symptoms and misdiagnosis.

In August 2010, alarms were raised in Scandinavian countries about an increase in the incidence rate of narcolepsy diagnosis in children and adolescents after September 2009. The pharmacovigilance authorities in Sweden and Finland were concerned that this increase in the number of narcolepsy cases may be associated with the use of the ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix) during the H1N1 (swine flu) pandemic in 2009 and 2010 [7,8]. Following these concerns, a cohort study was conducted in Finland and the results showed that there was a 13-fold increased risk of narcolepsy in children aged 4–19 y old who received the vaccination compared to unvaccinated children [9].

* Corresponding author.
E-mail address: A.R.Weighall@leeds.ac.uk (A.R. Weighall).

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Abbreviations

ADHD-RS	attention deficit hyperactivity disorder-rating scale
AS03	adjuvant system 03
CBCL	Achenbach child behaviour checklist
CDI	children's depression inventory
CPRS-R	Conners parent rating scale-revised
EDS	excessive daytime sleepiness
ICSD-3	International classification of sleep disorders-third edition
I.Q	intelligence quotient
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International database of prospectively registered systematic reviews in health and social care
PSG	polysomnography
QATSDD	quality assessment tool for reviewing studies with diverse design
SDQ	strength and difficulties questionnaire
WIAT-II	Wechsler individual achievement test – second edition

These concerns led to further investigations about the incidence of narcolepsy in Europe before, during and after the swine flu pandemic and vaccination campaigns [4,10,11]. Supporting the association, Miller et al. [10] found a significantly increased risk of narcolepsy in children who received the vaccine in England, consistent with the findings of the cohort study conducted in Finland. It has been estimated that globally more than 1000 children have developed narcolepsy following the vaccination [12]. Unfortunately official data on the incidence and prevalence of childhood narcolepsy (both for vaccine related and unrelated cases) are currently unavailable [13].

It is important to consider the effect narcolepsy may have on school-age children who are in a critical period for their physical, emotional and social development and their academic attainment. Given the recent increase in the number of children and adolescents diagnosed with narcolepsy, it is timely to systematically review, critically appraise and summarise the current quantitative and qualitative research that has investigated the consequences of this serious disorder in childhood. The review aims to update understanding of how cognitive function and psychosocial well-being in school-age children with narcolepsy compares with that of school-age children without narcolepsy and to assess what study designs and methods have been used to investigate this. The review also aims to assess the quality of the included studies and to provide recommendations for future research by highlighting gaps in the current evidence base.

Methods

A systematic review was conducted to assess whether cognitive function and psychosocial well-being is impaired in school-age children with narcolepsy. This review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 checklist and is registered in PROSPERO. The registration number is CRD42015018949 [14].

Literature search

Electronic databases were searched on 28th August 2015. The databases searched included; The Cochrane Library, Embase Ovid MEDLINE and PsycINFO (See Table 1). Records were downloaded and added to EndNote bibliography software. The records were de-duplicated.

The search was structured to combine the following concepts:

(Narcolepsy OR Cataplexy) AND (Children OR Adolescents) AND Cognition OR Psychosocial Well-Being.

Inclusion criteria

For this review one reviewer (JB) screened titles and abstracts. Another reviewer (HA) independently screened 5% of these articles in order to establish agreement about the inclusion and exclusion of studies. The website random.org was used to randomly select 5% of the articles and the inter-rater agreement was 98%. Any disagreements during this process were resolved by discussion and a consensus decision was reached.

Quantitative and qualitative research studies primarily concerned with narcolepsy (and cataplexy) in school-aged children (5–18 y old) and cognitive function or psychosocial well-being were eligible for inclusion in the review. Research studies written in English language and published in peer-reviewed journals between 2005 and 2015 were included in the review. Single case studies were excluded from this review. These criteria were selected so that only the most current research (published in the last decade), relevant research and high quality research was included within this review.

Full papers that were identified as potentially relevant were retrieved and screened in the same way as previously described based on the inclusion criteria and authors were contacted to clarify any missing information. Inter-rater agreement was 100%.

Data extraction

The Cochrane data extraction form was modified for the purposes of this review. Data were extracted into the standardised form by one researcher (JB) and authors were contacted when insufficient information was provided. 50% of these articles were then double data extracted by another researcher (HA). Any disagreements were resolved by discussion and a consensus decision was reached.

Quality assessment

Individual study quality was assessed with the 'quality assessment tool for reviewing studies with diverse design' (QATSDD) [15], a 16-item, validated quality assessment tool applicable to research with heterogeneous study designs (qualitative, quantitative and mixed methods). This tool was particularly suitable for assessing the quality of the papers included in this review as it encompasses an evaluation of both quantitative and qualitative aspects of research. Two reviewer's (JB and HA) independently awarded each research paper a quality score on a 4-point scale from 0 to 3 for each of the QATSDD criteria (0 = the criterion is totally undescribed, 1 = described to some extent, 2 = moderately described and 3 = described in full). An example criterion from the QATSDD is "description of procedure for data collection". As none of the studies included in this review employed mixed methods, only 14 out of the possible 16 quality assessment criteria were evaluated for each paper (as the remaining two criteria only address mixed-method research). For each paper, the sum of the 14 quality assessment scores indicated the overall quality of the paper (expressed as a percentage of the maximum possible score of 42). Additionally, an overall quality score was assigned for all studies using the same design (e.g., quantitative or qualitative studies) in order to assess the full body of evidence. To do this, an average of