Narcolepsy With or Without Cataplexy In The Pediatric Population: A Systematic Review

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Abstract

Study Objectives: Narcolepsy diagnosis has been associated with a long lag time between the onset of the disorder and the diagnosis itself among patients with the disorder. This article reviews the childhood epidemiology of idiopathic narcolepsy, including its prevalence, subtypes, and disease progression.

Methods: A literature review was conducted to include both published and unpublished data on pediatric narcolepsy. All English language articles were included through April, 2015.

Results: Time from symptom onset to diagnosis for children is approximately three years. The prevalence of cataplexy appears to be lower in children compared to adults, suggesting a later onset of cataplexy. The presence of cataplexy, however, was unrelated to demographic factors and laboratory findings.

Conclusion: There is a substantial lag-time between initial symptom presentation and diagnosis in children with narcolepsy. A less quintessential presentation of narcolepsy might occur in children relative to adults, making diagnosis more challenging. Continued improvements in narcolepsy education for both pediatricians and parents might facilitate earlier identification and diagnosis of the disease, thus leading to improved outcome.

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Introduction

Narcolepsy is an uncommon neurological disorder affecting 0.02-0.067% of the population\(^4\), although rates may vary with higher prevalence found in the Japanese population [0.16%]\(^2\) and lower prevalence in the Israeli population [0.002%]\(^3\). Narcolepsy is characterized by excessive daytime sleepiness (EDS) and/or sleep attacks. Narcolepsy is sometimes associated with vivid dreams, as well as other rapid eye movement (REM) phenomena such as sleep paralysis (SP), hypnagogic and/or hypnopompic hallucination, automatic actions and interrupted nighttime sleep. Although studies suggest a bimodal onset with peak incidence occurring around 15- and 36-years of age\(^5\), cases starting as young as 6-7 months have been reported\(^5\).

Challenges to diagnosing narcolepsy in the pediatric population include its atypical symptom presentation as it mimics other disorders (e.g., seizures and syncope), the need for naps in preschoolers as a normal entity masking narcolepsy, young children’s limited ability to self-report symptoms, children’s compensatory over-activity to self-stimulate (e.g., appearing to have attention deficit hyperactivity disorder\(^6\)), and a lack of knowledge about the disorder among many pediatric specialists\(^7\). Despite these challenges, however, there may be a shorter lag time to diagnosis following symptom onset among pediatric populations than among adult populations\(^7\). A few studies have focused specifically on narcolepsy’s presentation and progression in children; however, most reviews have not examined characteristics of those cases with vs. without cataplexy, partly due to the belief that some of those presenting with narcolepsy without cataplexy can later turn into those with cataplexy\(^8\). This current systematic review examines epidemiological and laboratory findings among pediatric populations while comparing narcolepsy with vs. without cataplexy, as cataplexy may moderate such findings.

Cataplexy, a common symptom of narcolepsy triggered by strong emotional stimuli, is characterized by a partial or total muscle weakness affecting the face, limbs or shoulders, but with retention of consciousness and normal respiratory and ocular muscle activity\(^9\). Narcolepsy with cataplexy (N+C) patients may be more apt to exhibit severe forms of the disorder and most often require additional medications to treat their cataplexy. The frequency of cataplectic episodes is thought to be worse at disease onset as it appears to later decrease\(^5\). In general, the episodes are of rapid onset, short duration and have bilateral presentation. Muscle atonia is also present during cataplectic episodes indicating postsynaptic hyper-polarization of the spinal cord\(^9\). N+C predominates in 85% of adult cases\(^1\).

Criteria for making a diagnosis of narcolepsy include the presence of EDS lasting more than three months\(^10\). This is in addition to cataplexy and either short sleep latency on a mean sleep latency test (MSLT; less than 8 minutes in adults and 12 minutes in children) or the presence of sleep onset rapid eye movements (SOREMs) in at least two of four or five naps after a nighttime sleep of at least six hours the previous night. According to the new International Classification of Sleep Disorders – third edition (ICSD-3) criteria, one SOREM can be replaced by fast onset of REM in preceeding sleep study (i.e., within 15 minutes of sleep onset)\(^11\). Narcolepsy without cataplexy (N-C) requires the same symptoms and evaluative test results as N+C but the patient lacks cataplexy symptoms, typically assessed by self report or parental observation of the phenomenon. In cases without short sleep latency, a low hypocretin-1 level on cerebrospinal fluid (CSF) analysis should be present (less than 110 ng/ml) to diagnose narcolepsy. However, in ICSD-3, narcolepsy is divided into type 1 (presence of cataplexy and/or low hypocretin levels in CSF) or type 2 (lack of cataplexy and either normal or undocumented hypocretin levels). Since most studies have relied on the older ICSD classification and almost all studies with N-C did not test for hypocretin level, the divisions used in this analysis used N+C (almost equivalent to type 1) and N-C (equivalent to type 2). Also of note, human leukocyte antigen (HLA) DPB*0601 is usually positive, especially among those diagnosed with N+C\(^12\). Other HLA phenotypes including HLA DR2 are sometimes positive as well, suggesting genetic vulnerability.

Although there is a genetic predisposition with concordance rates in monozygotic twins of 25-31%\(^3\), the lack of even higher concordance suggests that environmental causes also play a major role in the onset of narcolepsy. Immunological reaction secondary to
infection and/or immunization against hypothalamic cells, for example, has been proposed as an environmental factor that may precipitate narcolepsy, as demonstrated by elevated antistreptolysin O (ASO) and Anti DNAse (ADB) levels. Since one would expect urgency in treating this infection with antibiotics or other novel treatments like intravenous immunoglobulins, it is important to identify the extent of delay in diagnosis time in narcoleptic populations and factors associated with the rapid diagnosis of narcolepsy.

Differences in epidemiology, comorbid symptoms, and laboratory findings may exist in the presence vs. absence of cataplexy. The current review provides a systematic analysis and update of idiopathic narcolepsy and its subtypes in child studies, including data on the disease onset, time to diagnosis, and examination of epidemiological factors and laboratory findings for children with narcolepsy both with vs. without cataplexy. Specifically, we address the following three questions: 1) Do children with narcolepsy with vs. without cataplexy differ in age of onset, age of diagnosis, and gender distribution?; 2) do they differ in the presence of comorbid symptoms (e.g., hallucinations and sleep paralysis)?; and 3) do they differ on laboratory findings (i.e., polysomnographic parameters, HLA typing and hypocretin levels)?

Methods

A literature review was conducted by crossing the term "narcolepsy" with "children", "adolescent", and "pediatric" as well as searching for "childhood narcolepsy" in Pubmed, Ovid, Google Scholar, Scopus and EMBASE. To minimize potential publication bias effects, unpublished research (e.g., dissertations, theses and abstracts) was also reviewed. English language articles were included through April, 2015, while published data in other languages were excluded.

Inclusion and Exclusion Criteria

Studies that included data for children and/or adolescents aged less than 19 years were included. No published cases involving adults were included. Since secondary narcolepsy can affect the disease onset (e.g., due to brain tumor, and metabolic disorders such as Neiman-Pick, etc.), attempts were made to exclude this subgroup. Studies involving cases related to H1N1 infection were also excluded given the controversial role of H1N1 infection in narcolepsy. In addition, studies that did not differentiate parameters for N+C and N-C were excluded, as were studies that did not include disease progression. In order to minimize selection bias, single case reports were also excluded from this review. Finally, there were two studies involving infants and young children that were excluded because participants did not meet the full criteria for narcolepsy and the resulting inability to distinguish these children from those with primary hypersomnia, as well as due to the infant’s inability to substantiate any comorbid symptoms such as hypnagogic or hypnopompic hallucination or SP. However, a separate analysis was conducted involving the 11 participants from these two studies.

The following data were recorded from each article: children’s demographics (i.e., gender and age), disease progression (i.e., age of disease onset, symptom onset order, and age of diagnosis), prevalence of associated narcolepsy symptoms (i.e., hypnagogic and hypnopompic hallucinations and sleep paralysis), and the percentage of children who met criteria for narcolepsy with vs. without cataplexy (N+C vs. N-C).

Studies Analyzed

Of the 38 initially identified articles, 24 publications included children both with and without cataplexy; the other 14 included only those with cataplexy as researchers in these studies focused only on N+C. This was probably related to selection of the latter group and not necessarily related to the lack of individuals without cataplexy. However, since complete data was missing in some of the 24 studies, only the nine studies that included information on both subtypes of narcolepsy (i.e., those with and without cataplexy) constituted the core of our analyses, along with 10 of the 14 studies in the N+C study only group as they contained data on age of onset and age of diagnosis. The other 19 studies did not include this data and were excluded from analyses after attempts to contact the authors did not yield any further information. In addition, one study focusing on infants and very young children did not report the age of diagnosis and was thus excluded.
All cases presented with excessive daytime sleepiness at one point during the disease course. Percentages of the associated symptoms of cataplexy, hypnagogic or hypnopompic hallucination, and sleep paralysis were examined. Especially in cases lacking cataplexy or inconclusive cases, polysomnography (PSG) with mean sleep latency test (MSLT) is usually performed. However, controversy about the sensitivity and reliability of the MSLT exists\(^\text{47,48}\). Total sleep time (TST), sleep latency (SL), sleep efficiency (SE), REM latency (REML), stage 1, 2 and slow wave as well as REM percentage are also analyzed across each individual’s polysomnography. MSLT latency time and number of sleep onset REM (SOREM) were also examined. Since human leukocyte antigen (HLA) DQB*0602 (identified in 9 studies in cases with combined narcolepsy and in 8 studies including cases with narcolepsy with cataplexy) and HLA DRQ/ DRB*1501 (2 from combined narcolepsy and 3 from narcolepsy with cataplexy) have often been associated with a high incidence of narcolepsy, analysis of HLA positivity in these studies was also conducted. Finally, low cerebrospinal fluid hypocretin (less than 110 ng/ml) is pathognomonic for narcolepsy. However, due to the procedural invasiveness required to obtain hypocretin levels, it is less likely to be assessed but was included in three studies from the combined narcolepsy group and five from the narcolepsy with cataplexy group.

**Results**

**Question 1.** Do children with narcolepsy with vs. without cataplexy differ in age of onset, age of diagnosis, or gender distribution?

Of the 24 studies that included children with vs. without cataplexy, nine reported the age of symptom onset and the age of narcolepsy diagnosis. In addition, 10 of the 14 studies of children with only N+C also included this information (see Table 1). The number of children with narcolepsy who also had cataplexy was 63.6% (n = 63) across studies that specified co-occurrence of cataplexy, and 289 when adding those from all studies that included only N+C group, indicating that the majority of children with narcolepsy do have cataplexy. The mean age of onset of narcolepsy symptoms for the N+C group was highly similar to that of the N-C group (11.1 years, ± 3.0 vs. 11.1 years, ± 4.3, respectively) in the first nine studies (\(p = .99\)). Children in the N+C group were somewhat younger when examining only the 19 studies that reported symptom onset (10.4 years, ± 3.0). Overall, the mean age of onset for all narcolepsy patients (325 children) was 10.4 years (± 3.2).

The mean age of diagnosis for all children with N+C and N-C combined was 13.3 years (± 3.5). Some studies have suggested that the presence of cataplexy or worsening of symptoms may prompt seeking treatment and lead to an earlier diagnosis\(^\text{49}\). However, the similar age at symptom onset and diagnosis between the N+C and N-C groups suggests that this is not the case\(^\text{90}\). Specifically, age of diagnosis in the N+C group was 13.8 years (± 3.4) vs. 13.6 years (± 3.41) for the N-C group among studies containing both subgroups, a non-significant difference (\(p = .77\)), and 13.2 years (± 3.5) for the N+C group across all studies. Among the eight studies that included gender, females represented 43.5% (118/271) of cases in the N+C group and 37.5% (9/24) of cases in the N-C group, a non-significant difference (\(p = .67\)). The total combined percentage of females in both groups was 43.1% (127/295).

Analysis of studies containing the 11 infants was conducted separately\(^\text{47,48}\). Among this relatively small subgroup, a mean age of onset of 1.6 years (± 1.7) was found, but with a mean age of diagnosis of 6.1 years (± 2.4). Thus, time to diagnosis averaged 4.5 years for infants from the time of symptom onset, suggesting that narcolepsy may go undiagnosed for a longer period of time during early childhood. Cataplexy was present in only three of the 11 subjects (27.3%), suggesting that cataplexy is less common among those with narcolepsy in early childhood. Females represented five out of the 11 cases (45.5%), similar to the percentage among older children.

**Question 2.** Do children with narcolepsy with vs. without cataplexy differ in the presence of associated symptoms?

In the N-C group, 14 of the 36 individuals had hypnagogic and hypnopompic hallucination (38.9%) while 30 subjects of the 63 individuals in the N+C group from the 9 studies positive for hallucinations (47.6%), a non-significant difference (\(p = .53\)). In addition, sleep paralysis was present in 9 of 36 individuals in the N-C group (25.0%) compared to 19 of 63 in the N+C
Table 1: Descriptive statistics for studies reporting the age of symptom onset and the age of narcolepsy diagnosis among children

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Number</th>
<th>Average Age of Onset</th>
<th>Average Age of Dx.</th>
<th>Gender (% female)</th>
<th>HH%</th>
<th>Sleep Paralysis (%)</th>
<th>HLA DQB*0601</th>
<th>CSF Hypocretin</th>
<th>Country/year/age range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy in children, 1960&lt;sup&gt;15&lt;/sup&gt;</td>
<td>4</td>
<td>5.25 ± 2.87</td>
<td>10.25 ± 2.75</td>
<td>50% (2)</td>
<td>25% (1)</td>
<td>0% (0)</td>
<td></td>
<td></td>
<td>USA 1950-1957 3-14</td>
</tr>
<tr>
<td>Narcolepsy in children, 1991&lt;sup&gt;16&lt;/sup&gt;</td>
<td>4</td>
<td>11.33 ± 5.5</td>
<td>11.67 ± 6.03</td>
<td>0% (0)</td>
<td>50% (2)</td>
<td>50% (2)</td>
<td></td>
<td></td>
<td>USA/Brazil 6-18</td>
</tr>
<tr>
<td>Narcolepsy in children, 1993&lt;sup&gt;17&lt;/sup&gt;</td>
<td>2</td>
<td>9 ± 0</td>
<td>11 ± 0</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td></td>
<td></td>
<td>USA 1993</td>
</tr>
<tr>
<td>Narcolepsy in children, 2002&lt;sup&gt;18&lt;/sup&gt;</td>
<td>1</td>
<td>14 ± 0</td>
<td>17 ± 0</td>
<td>0% (0)</td>
<td>100% (1)</td>
<td>100% (1)</td>
<td></td>
<td></td>
<td>Belgium</td>
</tr>
<tr>
<td>A clinical picture, 1994&lt;sup&gt;19&lt;/sup&gt;</td>
<td>7</td>
<td>9.86 ± 2.85</td>
<td>13.71 ± 3.09</td>
<td>0% (0)</td>
<td>50% (1)</td>
<td>0% (0)</td>
<td></td>
<td></td>
<td>USA 7-12</td>
</tr>
<tr>
<td>Clinical and polysomn, 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2</td>
<td>13.5 ± 4.95</td>
<td>15 ± 5.66</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>66.7% (2)</td>
<td></td>
<td></td>
<td>India 2003-2010</td>
</tr>
<tr>
<td>Childhood onset, 2010&lt;sup&gt;21&lt;/sup&gt;</td>
<td>1</td>
<td>6 ± 0</td>
<td>11.5 ± 0.9</td>
<td>100% (1)</td>
<td>0% (0)</td>
<td>33.3% (1)</td>
<td></td>
<td></td>
<td>France 2010</td>
</tr>
</tbody>
</table>

Note. Age data presented are means and standard deviations. Dx= diagnosis; HH= Hypnagogic and hypnopompic hallucination; N+C= Narcolepsy with cataplexy; N-C= Narcolepsy without cataplexy.
group (30.2%), also a non-significant difference ($p = .65$).

EDS across groups was the primary presenting symptom in 46.0% (17/37) of cases in the 4 studies that included screening of the presenting symptoms at onset$^{2,51,53,57,61,71}$. Co-occurrence of both EDS and cataplexy was the second most common presentation in 37.8% of cases (14/37). Cataplexy by itself was the rarest initial symptom, occurring in only 16.2% (6/37) of cases. Among two studies reporting hallucinatory data, the mean age of onset for hypnagogic or hypnopompic hallucinations was 11.1 years, while the mean age of sleep paralysis across three studies was 10.3 years, similar to the mean age of onset of narcolepsy symptoms reported above$^{2,53,61}$.

**Question 3. Do children with narcolepsy with vs. without cataplexy differ on laboratory findings (i.e., polysomnographic parameters, HLA typing and hypocretin levels)?**

PSG parameters were reported in only two studies comparing N+C and N-C groups. In the N+C group (28 children), mean TST averaged 430.9 minutes ($\pm 51.5$) compared to 452.6 minutes ($\pm 46.7$) for the N-C group (16 children), a non-significant difference ($p = .17$). The average age for the studies at the time of PSG was the same for both groups: 14.8 $\pm$ 3.2 for N+C compared to 14.8 $\pm$ 3.9 for N-C. The total average TST for the N+C group including 179 subjects (seven studies) averaged 436.3 minutes ($\pm 72.3$). Sleep efficiency (SE) for the N+C group across the two studies was 88.3 minutes ($\pm 8.8$) compared to 90.1 minutes ($\pm 5.7$) for the N-C group, also a non-significant difference ($p = .47$). MSLT average sleep onset for the N-C group among 15 children was 4.6 $\pm$ 4.2 minutes compared to 3.8 minutes ($\pm 1.7$) for the six children in the N-C group who had MST data ($p = .69$). When including all 228 subjects with N+C across 11 studies, MSLT was 3.3 minutes ($\pm 2.8$). Average SOREM among three studies involving 15 children with N+C was 2.9 minutes ($\pm 1.2$) compared to 6.0 minutes ($\pm 0.6$) among the six children in the N-C group ($p = .88$).

Across three studies that examined the presence of the HLA DQB*0601 allele, 91.3% (21/23) of children in the N+C group compared to 78.6% (11/14) of the N-C group had a positive allele ($p = .35$), suggesting that most children are positive for the HLA DQB*0601. When including all N+C studies, 225 out of 236 children were positive for HLA DQB*0601 (95.3%).

CSF hypocretin levels were reported in five studies among the N+C group, with 45 out of 46 children (97.8%) exhibiting low hypocretin levels. The remaining child showed intermediate hypocretin levels. Hypocretin could not be examined among the N-C group as nearly all studies did not examine hypocretin levels in this population (a single child tested in one study showed low hypocretin levels).

**Discussion**

This systematic review examined the age of onset, age of diagnosis, and prevalence of narcolepsy symptoms suggesting a three year gap between the time of symptom onset and the time to diagnosis. Since immunological reaction of the disease is suspected, intravenous immunoglobulin has been proposed as a treatment; thus, the shorter duration to diagnosis is important to use this treatment modality$^{83}$. This three year gap, while still problematic, is significantly lower than the roughly 10 to 15 year gap between symptoms onset and diagnosis often found in the adult population$^7$.

Examining adults, factors such as country (i.e., among nine European countries, France had the shortest delay $^{[11.9]}$ compared to the longest in Spain $^{[21.1]}$) and year of study (i.e., before the 1940s, there was an average delay of 52.5 years with a gradual decrease in subsequent years, reaching about three years in the 1990s$^7$) may be important to consider when examining the time between symptom onset and diagnosis in children. On a positive note, the decreasing time to diagnosis over the decades among adults suggests improved patient and physician education about narcolepsy$^{30}$. Other factors potentially associated with delayed diagnosis among adults relative to children include year of first symptom, number of symptoms, and absence of cataplexy as a cause for delayed diagnosis$^{30}$. In contrast, we found that absence of cataplexy does not appear to be related to age of diagnosis among children. One adult study also found female gender to be associated with a longer time to diagnosis$^{91}$, while another found idiopathic hypersomnia to be associated with later diagnosis$^{92}$. Children with other sleep disorders (e.g., obstructive sleep apnea) often present
with symptoms of attention deficit hyperactivity disorder or depressive symptoms\textsuperscript{93,94}; thus, the presence of EDS in this younger population should raise suspicions about a possible diagnosis of primary hypersomnia or narcolepsy. In addition, children presenting with EDS often suffer academically and are usually identified early by teachers who observe their daytime sleepiness and academic deterioration. This is in comparison to adults, who may have greater compensatory mechanisms (e.g., drinking caffeinated beverages). In a study conducted in South China, N+C was found to have a bimodal distribution, with the first peak at age 11 coinciding with that found in our review, and the second peak at age 39\textsuperscript{95}. However, in the N-C group only one peak at about age nine years was found\textsuperscript{95}. Contrary to this study, we found that N+C age of onset was somewhat younger than among children with N-C (10.4 vs 11.1). It is interesting that only one patient had an early onset of EDS with later cataplexy after 15 years. This suggests a dramatic difference between N+C and N-C. This later study also found an earlier onset in females compared with males. However, we found a higher prevalence of males among both the N+C and N-C groups among young children.

Since most of these pediatric studies are retrospective and depend on patient or family recall of symptoms, it is not unexpected for EDS to be the most common presenting symptom due to its having the most disabling consequences. In our review, EDS was the presenting symptom in about 46% of cases, with co-occurring EDS and cataplexy the second most common presentation (38%) and cataplexy by itself the rarest initial symptom, occurring in only 16% of cases. When combing the EDS only and EDS/cataplexy groups, they represent 84% of cases. When it comes to the mean onset of symptoms of narcolepsy (cataplexy, hypnagogic and hypnopompic hallucination, and SP), cataplexy onset averaged 10.9 years of age, sleep paralysis 10.3 years, and hypnagogic or hypnopompic hallucinations 11.1 years. In addition, no characteristic difference (i.e., disease presentation and symptom progression) was found between N-C and N+C in our study.

In the current analysis, cataplexy was present among 64% of children with narcolepsy. This represents, however, a lower prevalence than found in most studies. For example, 80.5% of the 77 children diagnosed with idiopathic narcolepsy were found to have cataplexy in one study\textsuperscript{8}.

Although the characteristics of N+C vs. N-C were examined in the pediatric population, several other factors might contribute to the somewhat unique presentation of narcolepsy in children. For example, narcolepsy has a genetic predisposition, with a familial predisposition occurring in 10% of cases, and a concordance rate among monozygotic twins of 25-31\textsuperscript{96}. However, the lack of perfect concordance suggests a role for other factors. Thus, environmental factors including infectious etiologies and autoimmune reaction has been suspected and reported with up-to 5.4 times higher risk\textsuperscript{97}. For example, in a case study of an eight year old boy, a high ASO and ADB was found to be elevated after infection\textsuperscript{96}. Although infection symptoms improved, narcolepsy symptoms persisted and improved with stimulant medications. ASO was found to be elevated in 65% of children within one year of narcolepsy development compared to only 26% in controls\textsuperscript{98}. In yet another study, children born in winter time (mainly January) were 2.8 times more likely to develop narcolepsy\textsuperscript{95}.

There was no significant difference in the PSG and MSLT parameters between the N+C and N-C groups. However, HLA typing for DQB*0601 has been positive in 91-95% of the N+C group compared to 78% for those without cataplexy. This latter observation is well documented but its explanation unclear. In addition, it is important to note that most of the individuals with this haplotype do not express narcolepsy. Thus, HLA typing is an adjunct diagnostic tool but is not conclusive. CSF hypocretin level is a more reliable tool to diagnose the narcolepsy, but is unlikely to be performed. Children in the N+C group all had low or intermediate hypocretin levels, with 98% having low levels. Since hypocretin analysis was rarely conducted in the N-C group, it is difficult to comment on a possible difference between subtypes based on hypocretin levels. In one study in Brazil, all 14 adults with low hypocretin levels had cataplexy and positive HLA DQB*0601 typing. However, among 14 other adults with normal hypocretin levels, only 29% (four subjects) had cataplexy and their HLA was also positive. There was another 29% of these 14 who were negative for both cataplexy and HLA typing\textsuperscript{99}.
Thus, a combination of procedures may help to confirm suspected narcolepsy.

Several limitations of the current study deserve mention. While we attempted to delineate the characteristics of idiopathic narcolepsy with and without cataplexy in children, studies in our analysis were solely conducted when the diagnosis of narcolepsy was based on the second edition of the International Classification of Sleep Disorders\textsuperscript{100}, and distinguished between primary and secondary narcolepsy. This distinction was removed from the third edition in which narcolepsy type 1 may present with cataplexy and either PSG/MSLT findings or low hypocretin levels, while type 2 is characterized by a lack of cataplexy and normal or undetermined hypocretin levels (i.e., CSF hypocretin levels were never checked)\textsuperscript{101}. This classification change could potentially have biased results as those with N-C (or type 2) can develop with time/age to have cataplexy (N+C, or type 1)\textsuperscript{102}. Another limitation concerns the possible overdiagnosis of N-C given the lack of use of prior actigraphy or sleep logs (to exclude other causes of such as circadian rhythm problems and primary hypersomnia) as well as the lack of CSF hypocretin levels reported in most studies\textsuperscript{103}. Some authors argue that low CSF hypocretin is present in 10-30% of individuals and thus our distinction of N+C vs. N-C might not represent up to date classification as ICSD-3 of using type 1 vs type 2 since this might depend on hypocretin levels. In addition, while attempts were made to exclude secondary narcolepsy (e.g., Prader Willi, Niemann-Pick, brain tumor) in the current review, many of the publications did not specify if their population was idiopathic or secondary to other brain pathology. Less common subtypes of narcolepsy can occur secondary to neurological disorders including brain tumor, especially those affecting the hypothalamus\textsuperscript{104}, as well as trauma, genetic disorders (i.e., up to 36% of children with Prader Willi syndrome have co-morbid narcolepsy\textsuperscript{105}) or other metabolic diseases.

Further research on childhood narcolepsy is required. Since many of the existing studies are retrospective and the accuracy of the disease onset and progression might be biased by the parent’s recollection of their child’s symptoms, epidemiological studies following a large cohort of children prior to symptom onset are needed. In addition, existing studies are often of modest sample size and rely mostly on questionnaires rather than syndromic diagnosis (combined symptoms, PSG with MSLT, and CSF hypocretin level) confirmation, potentially limiting diagnostic accuracy. Improved narcolepsy education for both pediatricians and parents might facilitate earlier identification and diagnosis of the disease, thus leading to improved outcome. This might be especially important in cases due to infectious etiology as the long-term outcome of narcolepsy might improve with earlier treatment by antibiotics and even immunoglobulins.

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