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Potential immunological triggers for narcolepsy and idiopathic hypersomnia: Real-world insights on infections and influenza vaccinations

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ABSTRACT

Objective: It is hypothesized that narcolepsy type 1 (NT1) develops in genetically susceptible people who encounter environmental triggers leading to immune-mediated hypocretin-1 deficiency. The pathophysiologies of narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH) remain unknown. The main aim of this study was to collect all reported immunological events before onset of a central disorder of hypersomnolence.
Methods: Medical records of 290 people with NT1, and 115 with NT2 or IH were retrospectively reviewed to extract infection and influenza vaccination history. Prevalence, distribution of immunological events, and time until hypersomnolence onset were compared between NT1 and the combined group of NT2 and IH.
Results: Immunological events were frequently reported before hypersomnolence disorder onset across groups. Flu and H1N1 influenza vaccination were more common in NT1, and Epstein–Barr virus and other respiratory and non-respiratory infections in NT2 and IH. Distributions of events were comparable between NT2 and IH. Rapid symptom onset within one month of infection was frequent across groups, especially after flu infection in NT1. Hypersomnolence disorder progression after an immunological event was reported in ten individuals.
Conclusions: Our findings suggest a variety of immunological triggers potentially related to NT1, including H1N1 influenza infection or vaccination, infection with other flu types, and other respiratory and non-respiratory infections. Frequent reports of immunological events (other than those reported in NT1) immediately prior to the development of NT2 and IH support the specificity of triggers for NT1, and open important new research avenues into possible underlying immunological mechanisms in NT2 and IH.

1. Introduction

Central disorders of hypersomnolence are primary neurological disorders characterized by excessive daytime sleepiness (EDS) [1]. These diagnostic entities are currently identified, narcolepsy type 1 and 2, and idiopathic hypersomnia [2]. Narcolepsy type 1 arises from a complex interaction of predisposing genetic and environmental factors leading to autoimmune-mediated hypocretin-1 deficiency, which instigates the development of cataplexy [1]. In narcolepsy type 2 and idiopathic hypersomnia, hypocretin-1 levels are normal, and cataplexy is absent. Narcolepsy type 1 and type 2 present rapid onset of rapid eye movement sleep during the polysomnography (PSG) and/or multiple sleep latency test (MSLT), which is not recurringly seen in idiopathic hypersomnia [2]. Long-lasting non-refreshing naps with sleep inertia and substantially prolonged nocturnal sleep are often associated with idiopathic hypersomnia [3].

Investigations following the surge in narcolepsy type 1 incidence rates after the H1N1 pandemic in 2009–2010 provided insights into potential environmental triggers for developing narcolepsy [4–12]. The H1N1 influenza vaccine Pandemrix (GlaxoSmithKline Biologicals,

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Wavre, Belgium) has been linked to narcolepsy type 1 [5,9–11] in several European countries. No other vaccines have been implicated to contribute to the pathophysiology of narcolepsy type 1. A similar increase in incidence was noted in Asian countries and the United States, where Pandemrix was not in use, so a putative viral infection was assumed responsible [4,6–8,12–14]. The relative absence of H1N1 infections between the 1918 Spanish flu and the 2009-2010-H1N1 pandemics suggests that other triggers may be involved in developing narcolepsy [15]. Multiple studies have proposed streptococcus pyogenes infections, as recent infections, elevated antibody levels and steptococcus-associated Sydenham chora have been reported close to narcolepsy type 1 onset [16–22]. Traumatic brain injuries have also been associated with EDS and low hypocretin-1 levels without cataplexy, but this phenotype often disappeared within six months with normalizing hypocretin-1 levels [23]. Case reports and series have reported Guillain-Barre syndrome [24], Wernicke's encephalopathy [25], tumors affecting the hypothalamus [26], and multiple sclerosis [27] lesions sporadically triggering secondary narcolepsy.

There is limited evidence on the common latency between infection and the development of narcolepsy. Case reports suggested this could be days [9,17]. In contrast, recent studies investigating the prevalence of H1N1 vaccination in people with narcolepsy indicated that this latency could be several months or even years [12,13,28]. Such differences in latency have previously been attributed to the multiple hit hypothesis, where genetically susceptible people must experience multiple triggers before they develop narcolepsy symptoms [1]. For some people, H1N1 vaccination could have been the trigger contributing to (but not yet) reaching the threshold for developing narcolepsy symptoms. In contrast, for others with possibly greater susceptibility (or multiple previously experienced triggers), H1N1 vaccination could have been the trigger that was strong enough to trigger the development of narcolepsy. H1N1 vaccination and infection have mainly been reported before narcolepsy development in children [9,12,14]. Following the multiple hit hypothesis in which potential triggers may have a cumulative effect on narcolepsy development, this suggests that H1N1 must be a relatively strong trigger. Analyses focused on this delay by monitoring individuals with hypersomnolence disorders could provide insights into the relationship between infections and/or vaccinations and the development of narcolepsy.

The pathophysiologies of narcolepsy type 2 and idiopathic hypersomnia remain unknown [29]. No significant incidence increases were reported for either disorder following the 2009-2010-H1N1 pandemic. A recent report of ten individuals with idiopathic hypersomnia found all had positive Epstein–Barr virus (EBV) serology, although none reported symptomatic infection just before hypersomnia onset [30]. The current hypothesis, therefore, is that an autoimmune mechanism does not cause narcolepsy type 2 and idiopathic hypersomnia.

We aimed to cross-sectionally investigate the distribution of potential immunological events in narcolepsy type 1 and 2, and idiopathic hypersomnia. Data were obtained from semi-structured interviews conducted during intake for all individuals reporting EDS and verified through external medical correspondence whenever possible. As well as the type of vaccination or infection, we identified the delay between the reported immunological events and the development of narcolepsy symptoms. Spontaneously reported non-immunological life events were also described. We hypothesized that immunological events, especially H1N1 vaccination and flu infections, would be more common in narcolepsy type 1 than in non-hypocretin-1 deficient hypersomnolence disorders.

2. Material and methods

2.1. Data collection

All people who attended the tertiary sleep-wake clinic Sleep-Wake Center SEIN Heemstede with a central disorder of hypersomnolence diagnosis between January 2010 and January 2020 were included in this observational study. Infection/influenza vaccination history was integrated into our semi-structured clinical interview since the 2009-2010-H1N1 pandemic in people who newly visited the clinic complaining of EDS. The infection and vaccination history were documented during this intake interview. Complete medical records were reviewed, and detailed data were extracted on infections, influenza vaccinations, symptoms (EDS presence and date of onset, cataplexy presence and onset), sleep test results (MSLT mean sleep latency and sleep-onset rapid eye movement period [SOREMP] count, and polysomnography SOREMP presence), objective biomarkers (CSF hypocretin-1 levels, and HLA-DQB1*0602 positivity) and Epworth sleepiness scale (ESS) scores. Correspondence from other healthcare providers (often the general practitioner) was generally available and in a substantial portion of subjects the infection/vaccination history was verified with the included medical history.

The extracted infection/influenza vaccination history included the infection/influenza vaccination type and its timing. Our analysis incorporated all infections and influenza vaccinations that occurred prior to the onset of the hypersomnolence disorder, without considering possible subjective beliefs on causality. Only people with a known infection and influenza vaccination history were included and our statistical analyses specifically focussed on immunological events before the onset of the hypersomnolence disorder. Infections were identified through clinical diagnosis and/or laboratory testing. If there was no formal diagnosis of the infection, then the symptoms experienced were extracted. Subjects were excluded from further analyses if the onset dates of EDS and cataplexy (in the case of narcolepsy type 1) were unknown.

We separately described other (non-infectious) life events reported before the onset of the central disorder of hypersomnolence and immunological events reported before the substantial worsening (disease progression) of the symptoms of the hypersomnolence disorder. Disease progression was defined as an immunological event followed by a physician-verified increase in EDS or cataplexy (in frequency or intensity) or the development of EDS or cataplexy as a new hypersomnolence disorder symptom. Subjects were not routinely asked for non-infectious life events before onset or events prior to worsening of their central disorder of hypersomnolence. The non-infectious events and events before hypersomnolence disorder worsening were spontaneously reported by the subject and stricter rules for inclusion therefore applied. Other life events and/or progression of the hypersomnolence disorder were not included in the statistical analyses and only described if the event occurred within one month of the change in the hypersomnolence disorder.

The Medical Ethical Committee of the VU Medical Center scrutinized the study. It consisted of an analysis of previously acquired clinical data posing no risk to people, so the study was exempted from the need to obtain individual consent. The clinical experiments conformed to the principals outlined by the Declaration of Helsinki. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for cross-sectional studies guidelines [31].

2.2. Diagnostic groups

Hypersomnolence diagnoses had to comply with ICSD-3 criteria [2]. Individuals included were classified as having narcolepsy type 1 or 2, or idiopathic hypersomnia. Those with a clear complaint of EDS but without fulfilling ICSD-3 diagnostic criteria were included as people with a "clinical diagnosis". Appendix A shows an overview of the clinical diagnosis groups' definitions and the implemented outcome measures. We repeated the analyses without the people with a clinical diagnosis in Appendix B to investigate whether this group had substantially influenced our results.

2.3. Data processing

Immunological event histories of people with narcolepsy type 1 were compared with a combined group of people with narcolepsy type 2 and idiopathic hypersomnia. Tree structures were built on infection and influenza vaccination history for both groups. Each tree consisted of three branches of leaves, each consecutively representing smaller subgroups of the full sample. The number of people were reported per leaf together with their HLA-DQB1*0602 statuses. Individuals were first branched based on whether they reported infection or influenza vaccination before developing their hypersomnolence disorder (first leaf). People in whom an infection and influenza vaccination were reported were included in the event group closest to their hypersomnolence onset. When both events were equally close to hypersomnolence onset, this individual was included in both analyses on infections and influenza vaccinations. The group with a reported infection was then subdivided into flu, EBV, other respiratory, and other non-respiratory infections (second leaf). For vaccination history the group was split into H1N1 influenza vaccination (in 2009–2010) and other types of influenza vaccination. The third branch separated based on the latency between the reported event and the onset of the hypersomnolence disorder (third leaf). This was grouped into hypersomnolence disorder start within or over one year after the reported immunological event, with occurences within one year regarded as rapid onset. The precise timing of the immunological event and onset of the hypersomnolence disorder were not known in all individuals. If known, the latency between the event and hypersomnolence disorder onset was often much shorter than one year. We therefore separately also reported prevalences of latencies within one month for each immunological event type. For people with narcolepsy type 1, we additionally described whether the progression between the onset of the EDS and cataplexy was within or over one year, with further subdivision per immunological event type.

Statistical analyses were performed on demographics and diagnostic criteria comparing narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia. Shapiro–Wilk normality tests were first used to test the distributions of the numerical variables in each subgroup, and one-way ANOVA or Kruskal-Wallis tests were used to compare the variables among the three subgroups depending on whether the data were normally distributed. The distribution of different immunological event types, prevalence of reported infections and influenza vaccinations were compared between people with narcolepsy type 1 and the non-hypocretin-1 diagnoses combined using Chi-Square tests, with subsequent analyses on the individual event types. Fisher's exact tests were used for group comparisons with fewer than five observations per outcome option. We estimated odds ratios and effect sizes. P-values were reported after multiple comparisons correction using the Benjamini–Hochberg procedure to decrease the false discovery rate to 0.05.

3. Results

We included 194 out of 290 people with narcolepsy type 1, 18 out of 28 people with narcolepsy type 2 and 54 out of 87 people with idiopathic hypersomnia based on the availability of onset of hypersomnolence complaints and data on infections and/or influenza vaccination. Clinical characteristics of the populations with known infection and/or influenza vaccination history are presented in Table 1. Typical clinical profiles for narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia were seen.

3.1. Immunological events before narcolepsy type 1 onset

Infection and/or influenza vaccination history was known in 194 people with narcolepsy type 1, of whom the infection history was known in 149 (Fig. 1A) and the influenza vaccination history in 142 (Fig. 1B). An infection and/or influenza vaccination were reported before developing narcolepsy type 1 in 87/194 individuals (44.8%). Thirteen individuals reported both an infection and influenza vaccination before the onset of their symptoms. These individuals were included in Fig. 1 in the group of the immunological event closer to their start of narcolepsy type 1 symptoms (for five people, this was an infection and five influenza vaccination). In the remaining three, the infection and influenza vaccination were similarly close to narcolepsy type 1 onset and they were included in both the infection and influenza vaccination groups.

3.1.1. Infection history

An infection before onset of narcolepsy type 1 symptoms was reported in 46/149 (30.9%; Fig. 1A). Flu was reported most (13/149, 8.7% of total sample), followed by EBV (12/149, 8.1% of total sample), other non-respiratory infections (11/149, 7.4% of total sample), and other respiratory infections (10/149, 6.7% of total sample). Other reported respiratory infections included pharyngitis (N = 3), pneumonia (N = 3), rhinitis (N = 1), tonsilitis (N = 1), bronchitis (N = 1), not further specified (N = 1), and other types of non-respiratory infections, included fever of unknown origin (N = 3), erysipelas (N = 1), enterovirus (N = 1), hip osteoarthritis (N = 1), toxoplasmosis (N = 1), otitis (N = 1), dengue (N = 1), not further specified (N = 2). Rapid onset of narcolepsy type 1 within one year after the infection was seen in 36/46 (78.3%) of all people who had reported infection and was most common for flu (13/13, 100%), followed by other respiratory infections (8/10, 80.0%), EBV (8/12, 66.7%) and other non-respiratory infections (7/11, 63.6%). Narcolepsy type 1 progression (delay between EDS and cataplexy onset) was

Table 1
Population characteristics.

Variable	Narcolepsy type 1 (N = 194)		Narcolepsy type 2 (N = 18)		Idiopathic hypersomnia (N = 53)		p-value
	N	Median (IQR)/Percentage	N	Median (IQR)/Percentage	N	Median (IQR)/Percentage	
Gender (female)	194	51.0%	18	72.2%	53	58.5%	0.1717
Age at onset EDS (years)	183	13.1 (10.0–18.0)	17	16.7 (15.7–24.0)	45	17.0 (14.5–20.9)	<0.0001
Cataplexy presence	194	94.8%	18	0.0%	53	0.0%	<0.0001
Age at onset cataplexy (years)	149	15.0 (11.2–23.0)	–	–	–	–	–
MSLT sleep latency (minutes)	159	4.0 (2.4–6.0)	17	5.0 (2.8–7.2)	52	6.9 (5.7–9.1)	<0.0001
Total number of SOREMPs	170	4.0 (2.0–5.0)	17	3.0 (2.0–5.0)	52	0.0 (0.0–0.0)	<0.0001
MSLT SOREMP number	170	3.0 (2.0–4.0)	17	3.0 (2.0–4.5)	52	0.0 (0.0–0.0)	<0.0001
PSG SOREMP presence	185	57.8%	18	50.0%	52	1.9%	<0.0001
MSLT REM latency (minutes)	123	3.9 (2.3–6.0)	16	5.2 (2.4–7.2)	1	13.5	0.2717[#]
CSF hypocretin-1 levels (pg/mL)	82	<40: 65.9% 40-110: 24.4% >110: 9.8%	6	<40: 0% 40-110: 0% >110: 100%	5	<40: 0% 40-110: 0% >110: 100%	<0.0001
HLA-DQB1*0602 positivity	156	98.1%	15	80.0%	38	21.1%	<0.0001
ESS score	111	16.0 (12.0–18.0)	14	16.0 (12.8–16.3)	44	15.0 (12.0–18.8)	0.9271

N reflects the available data for the corresponding variable. [#] The idiopathic hypersomnia group was not incorporated in this analysis and a Mann-Whitney *U* test was performed. EDS: Excessive daytime sleepiness; MSLT: multiple sleep latency test; PSG: polysomnography; SOREMP: sleep-onset rapid eye movement period.

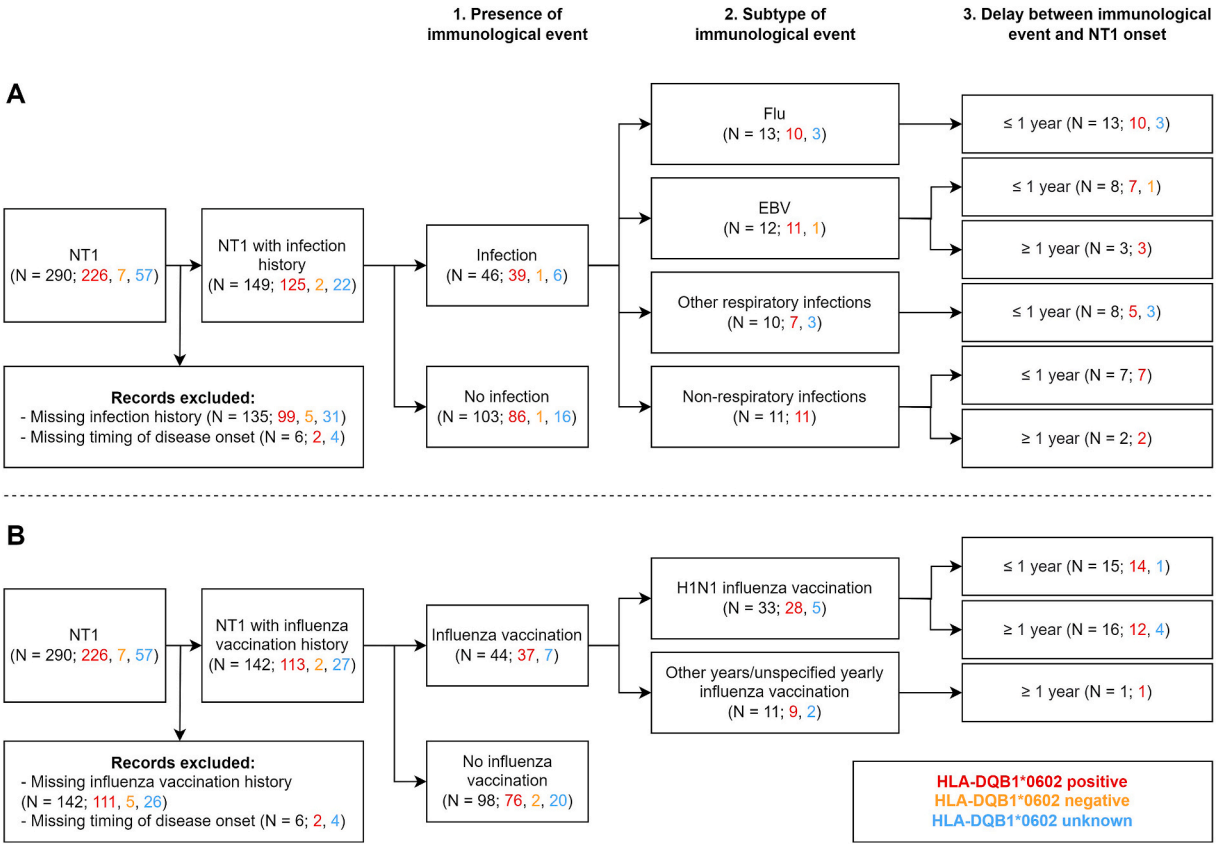

Fig. 1. Immunological events overview for narcolepsy type 1. If no exact timing of the immunological event was known, this individual was not included in column 3. EBV: Epstein–Barr virus; NT1: narcolepsy type 1.

within one year in 11/13 (84.6%) people with a reported flu infection, and less frequent for EBV (2/12, 16.7%), other respiratory (7/10, 70.0%) and other non-respiratory infections (4/11, 36.4%).

3.1.2. *Vaccination history*

Influenza vaccination was reported in 44/142 (31.0%) people with narcolepsy type 1 with a known influenza vaccination history. H1N1 influenza vaccination in 2009–2010 was reported in 33/142 (23.2%) of the total sample and 33/44 of all reported influenza vaccinations (75.0%). Eleven people received influenza vaccination in other years or on a yearly basis without specification in which exact years (7.7% of total sample and 25.0% of all influenza vaccinations). Of the people with H1N1 influenza vaccination, eight reported they had received Pandemrix vaccination and two Focetria. Rapid onset of narcolepsy within one year of the influenza vaccination was reported in 15/44 (34.1%) for those who received influenza vaccination, 15/33 (45.5%) for those with 2009–2010H1N1 vaccination and in 0/11 (0.0%) for others. A short delay between the onset of EDS and cataplexy was frequently seen in the H1N1 influenza vaccination group (25/33, 75.8%) compared to influenza vaccination in other or unspecified years (4/11, 36.4%).

3.1.3. *Onset of narcolepsy type 1 within one month after an immunological event*

For people reporting an infection the exact timings were known in 27 individuals, of whom 20 individuals developed narcolepsy type 1 symptoms within a month of the infection. These reported infections included flu (N = 8), EBV (N = 4), fever of unknown origin (N = 2), pharyngitis (N = 1), pneumonia (N = 1), tonsillitis (N = 1), rhinitis (N = 1), otitis (N = 1) and enterovirus (N = 1). The exact timings were known in 23 individuals in the influenza vaccination group; two people (8.7%) developed narcolepsy type 1 symptoms within one month after their H1N1 influenza vaccination.

3.1.4. *Disease progression*

Narcolepsy type 1 progression was also reported concerning immunological events. Six people who already had EDS reported cataplexy development after an immunological event (two people after flu infection, two after pharyngitis, one after an EBV infection and one after H1N1 influenza vaccination). EDS development in people with cataplexy was reported in two people after an immunological event (one person after an EBV infection and one after H1N1 influenza vaccination). Substantial worsening of EDS complaints after an immunological event was reported in one person after H1N1 influenza vaccination.

3.1.5. *Other life events*

Multiple other life events before narcolepsy symptom onset (that were not part of the semi-structured clinical interview) were also sporadically reported in the medical records and included traumatic brain injury (N = 3), childbirth (N = 1), increased anti-GAD34 levels (N = 1), human papillomavirus (HPV) vaccination (N = 4), combined diphtheria, pertussis, tetanus, polio and hepatitis A vaccination (N = 1), hepatitis B vaccination (N = 1), combined hepatitis A and B vaccination (N = 1) and unspecified holiday vaccinations (N = 1).

3.2. *Immunological events before narcolepsy type 2 and idiopathic hypersomnia onset*

Infection and/or influenza vaccination history was known in 71 individuals with narcolepsy type 2 or idiopathic hypersomnia, of whom the infection history was known in 44 (Fig. 2A) and the influenza vaccination history in 57 (Fig. 2B). Infection and/or influenza vaccination were reported before developing narcolepsy type 2 or idiopathic hypersomnia in 36/71 individuals (50.7%). Among the people with narcolepsy type 2 or idiopathic hypersomnia, there were six individuals who reported an infection and influenza vaccination before onset of

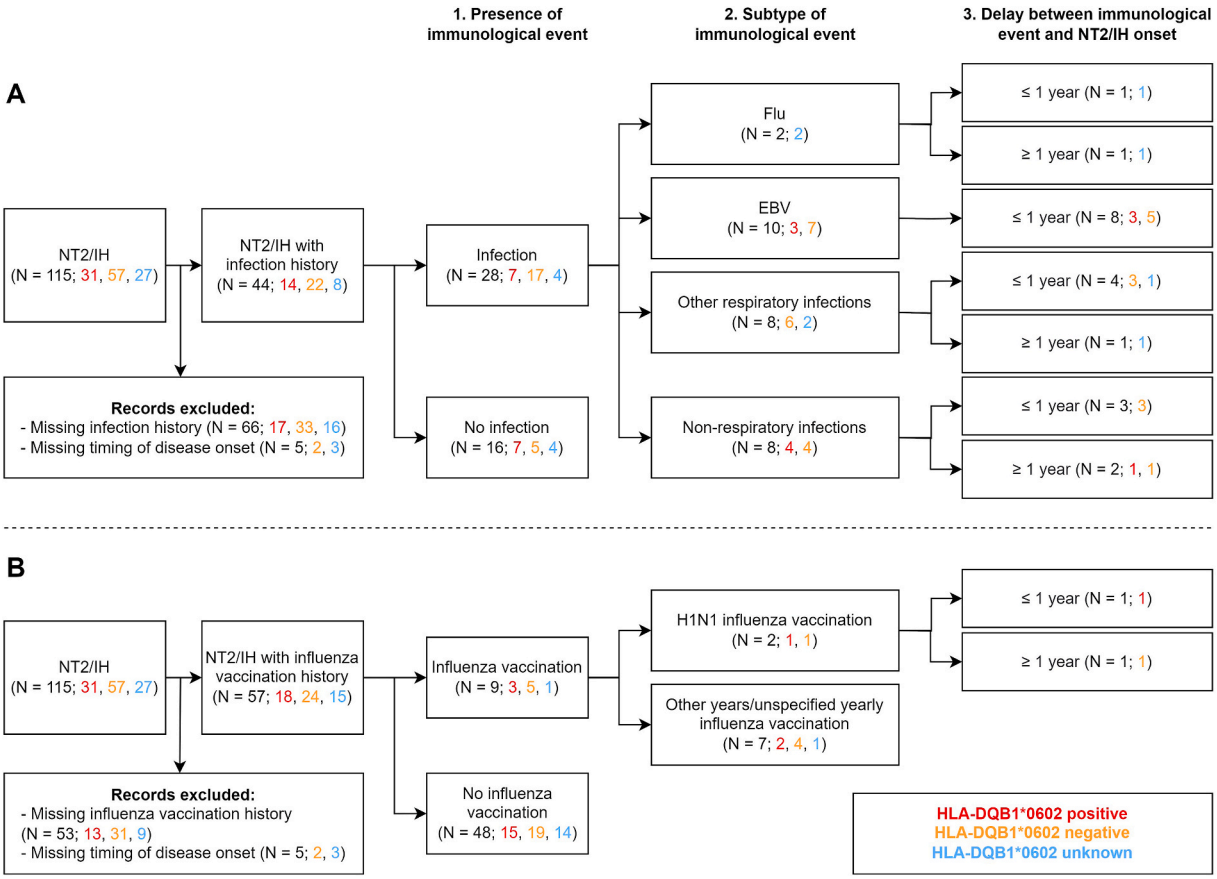

Fig. 2. Immunological events overview for narcolepsy type 2 and idiopathic hypersomnia. If no exact timing of the immunological event was known, this individual was not included in column 3. EBV: Epstein–Barr virus; IH: idiopathic hypersomnia; NT2: narcolepsy type 2.

their hypersomnolence disorder. These individuals were included in Fig. 2 in the group of immunological events closest to their start of EDS (for five people this was an infection). In one person, the infection and influenza vaccination were similarly close to EDS onset and this individual was included in the infection and influenza vaccination groups. The limited group sizes of narcolepsy type 2 and idiopathic hypersomnia do not allow for statistical comparisons between subgroups but both diagnoses contributed similarly to the reported infections and influenza vaccinations.

3.2.1. *Infection history*

An infection before onset of narcolepsy type 2 or idiopathic hypersomnia was reported in 28/44 (63.6%; Fig. 2A). EBV was reported most (10/44, 22.7% of total sample), followed by other respiratory infections (8/44, 18.2% of total sample), other non-respiratory infections (8/44, 18.2% of total sample) and flu (2/44, 4.5% of total sample). Other respiratory infections reported included pharyngitis (N = 2), allergic rhinitis (N = 1), allergic bronchitis (N = 1), pneumonia (N = 1), cmv (N = 1), scarlet fever with fever, sore throat, skin rash and secondary pyelonephritis (N = 1) and (unspecified) pulmonary infection (N = 1). Non-respiratory infections included fever of unknown origin (N = 2), appendicitis (N = 2), cholecystitis (N = 1), pyelonephritis (N = 1), meningitis (N = 1) and otitis (N = 1). Onset of narcolepsy type 2 or idiopathic hypersomnia within one year of the immunological event was seen in 16/28 (57.1%) of all people who reported an infection and was most common for EBV (8/10, 80.0%), followed by other respiratory infections (4/8, 50.0%), flu (1/2, 50.0%) and other non-respiratory infections (3/8, 37.5%).

3.2.2. *Vaccination history*

Influenza vaccination was reported in 9/57 (15.8%) people with narcolepsy type 2 or idiopathic hypersomnia with a known influenza vaccination history. H1N1 influenza vaccination in 2009–2010 was reported in 2/57 (3.5%) of the total sample and 2/9 of all reported influenza vaccinations (22.2%). Seven people received influenza vaccination in other years or yearly without specification of which exact years (12.3% of the total sample and 77.8% of all influenza vaccinations).

3.2.3. *Onset of narcolepsy type 2 or idiopathic hypersomnia within one month after an immunological event*

Eight individuals with narcolepsy type 2 or idiopathic hypersomnia developed EDS symptoms within one month of the infection. These reported infections included flu (N = 1), EBV (N = 3), fever of unknown origin (N = 1), pharyngitis (N = 1), scarlet fever with secondary pyelonephritis (N = 1), cholecystitis (N = 1). The exact timings were not known in the influenza vaccination group.

3.2.4. *Disease progression*

Substantial worsening of EDS complaints was reported by one person with idiopathic hypersomnia (who already had EDS) after pharyngitis.

3.2.5. *Other life events*

Other life events that occurred before symptom onset of narcolepsy type 2 or idiopathic hypersomnia that were not part of the semi-structured clinical interview were brain trauma (N = 2), sarcoidosis (1), morbus Scheuermann with chronic pain (1), childbirth (1) and anorexia nervosa (1).

3.3. Cross-disorder comparisons

Rate differences were compared between groups with odds ratios in Table 2 and Fig. 3. A full overview of all between-group comparisons is in Appendix C. In summary, people with narcolepsy type 1 and those with type 2 or idiopathic hypersomnia reported a similar overall prevalence of an immunological event before symptom onset (Fig. 3A) (odds ratio [95% confidence interval]: 0.79 [0.46–1.36], corrected p-value = 0.5073). The distribution of immunological events significantly differed between groups (Fig. 3B). People with narcolepsy type 2 or idiopathic hypersomnia reported a considerably higher absolute prevalence of infections than those with narcolepsy type 1 (odds ratio [95% confidence interval]: 0.26 [0.13–0.52], corrected p-value = 0.0020), mainly driven by reports of EBV and other respiratory and non-respiratory infections. Compared to different infection types, flu was relatively more frequent than other infections in people with narcolepsy type 1. Despite infections being more frequently reported in narcolepsy type 2 and idiopathic hypersomnia, onset of the hypersomnolence disorder within one year after the infection had a tendency to be more common in narcolepsy type 1 (odds ratio of onset within one year/onset over one year [95% confidence interval] is 2.7 [0.97–7.53], corrected p-value = 0.1127). This was mainly driven by people who reported a flu infection that developed narcolepsy type 1 within one year. H1N1 influenza vaccination was significantly more prevalent in people with narcolepsy type 1 (odds ratio [95% confidence interval]: 8.32 [1.93–35.98], corrected p-value = 0.0048).

4. Discussion

Immunological events before disease onset were frequently reported across central disorders of hypersomnolence. The distribution of immunological events differed between people with narcolepsy type 1, and those with narcolepsy type 2 or idiopathic hypersomnia. In people with narcolepsy type 1, flu infections and H1N1 influenza vaccinations were most common, but other infection types were also reported. In people with narcolepsy type 2 or idiopathic hypersomnia, EBV, other respiratory and non-respiratory infections were often reported, while influenza vaccinations were uncommon. Onset within one year of the potential trigger was frequently reported in both groups but tended to be more common in people with narcolepsy type 1. Flu infection, in particular, was associated with rapid onset of EDS and cataplexy, often within a month.

The variety of immunological events in narcolepsy type 1 replicate previously associated H1N1 infection [4,6–8], streptococcal infection [16–22], and Pandemrix vaccination [5,9–11] as potential immunological triggers. New potential triggers were also identified, including EBV and other upper respiratory and non-respiratory infections. These infections are common in the general population, but in our data, they frequently occurred within days to weeks before the onset of narcolepsy type 1. Thus, a direct relationship seems plausible. If we look for immunological commonalities among these infections, most involved the respiratory system and febrile illnesses were frequently seen. Reports of flu infections directly before narcolepsy type 1 onset in years where H1N1 was not the dominant flu strain within the Netherlands raise the question whether other flu strains (such as type B influenza or type A H3N2) could also be responsible for triggering narcolepsy type 1. More recently, questions have also arisen about the potential of COVID-19 infection and/or vaccination to trigger narcolepsy type 1. Future research should unravel this relationship and identify specific pathogens responsible for triggering narcolepsy type 1.

Surprisingly, we found frequent infections before the onset of narcolepsy type 2 and idiopathic hypersomnia. This provides new insights

Table 2
Between-group immunological events comparisons.

Variable	Narcolepsy type 1 (N = 194)		Narcolepsy type 2 or idiopathic hypersomnia (N = 71)		Odds ratio (95% CI)	Effect size	Corrected p-value
Infections & influenza vaccinations	N	Percentage of N	N	Percentage of N			
Total immunological events prevalence	194	44.8%	71	50.7%	0.79 (0.46–1.36)	0.0520	0.5073
Distribution of immunological events	90	Flu: 14.4% EBV: 13.3% Other respiratory infection: 11.1% Other non-respiratory infection: 12.2% H1N1 influenza vaccination: 36.7% Other years/unspecified yearly: 12.2%	37	Flu: 5.4% EBV: 27.0% Other respiratory infection: 21.6% Other non-respiratory infection: 21.6% H1N1 influenza vaccination: 5.4% Other years/unspecified yearly: 18.9%	–	0.3797	0.0193
Infections							
Total Infection prevalence	149	30.9%	44	63.6%	0.26 (0.13–0.52)	0.2827	0.0020
Flu infection prevalence	149	8.7%	44	4.5%	2.01 (0.44–9.26)	0.0655	0.6062#
EBV infection prevalence	149	8.1%	44	22.7%	0.30 (0.12–0.75)	0.1937	0.0273
Other respiratory infection prevalence	149	6.7%	44	18.2%	0.32 (0.12–0.88)	0.1655	0.0707
Other non-respiratory infection prevalence	149	7.4%	44	18.2%	0.36 (0.13–0.96)	0.1521	0.0854
Rapid onset after any infection	46	78.3%	28	57.1%	2.70 (0.97–7.53)	0.2241	0.1127
Influenza vaccinations							
Total influenza vaccination prevalence	142	31.0%	57	15.8%	2.40 (1.08–5.31)	0.1554	0.0815
H1N1 influenza vaccination prevalence	142	23.2%	57	3.5%	8.32 (1.93–35.98)	0.2343	0.0048#
Rapid onset after influenza vaccination	44	34.1%	9	11.1%	4.14 (0.47–36.25)	0.1879	0.4395#

N reflects the available data for the corresponding variable. # Fisher's exact test was performed. CI: confidence interval.

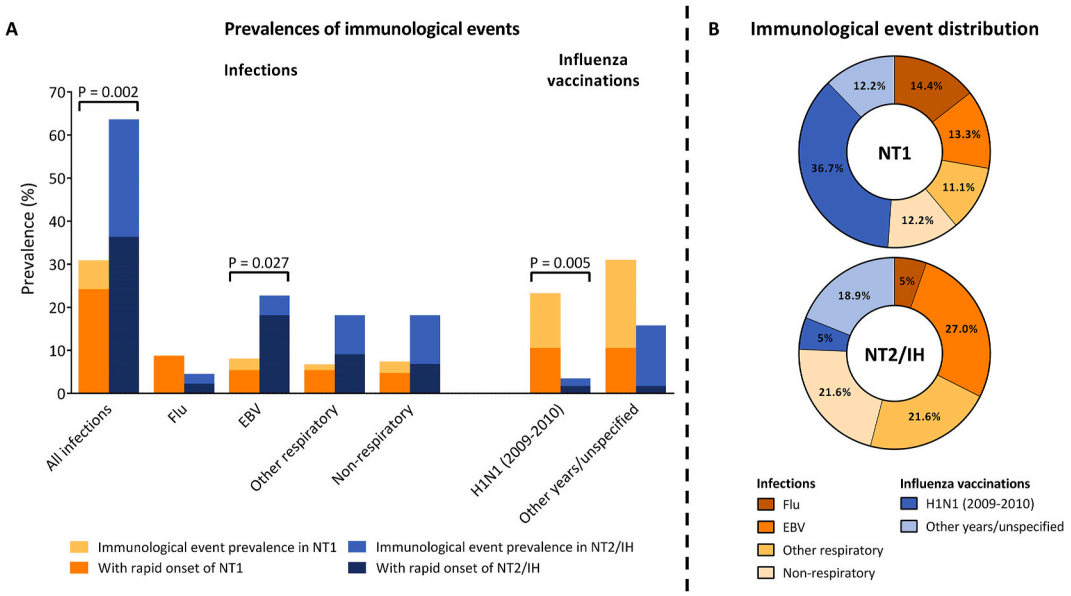

Fig. 3. Prevalences and distribution of immunological events per group. (A) Absolute prevalences of immunological events, split for rapid onset (within one year) and non-rapid onset of the central disorder of hypersomnolence. Significant between-group differences are displayed with corrected p-values. (B) Relative distribution of immunological events per group which is significantly different between groups (p = 0.0193). EBV: Epstein–Barr virus; IH: idiopathic hypersomnia; NT1: narcolepsy type 1; NT2: narcolepsy type 2.

into the potential of immunological pathophysiology underlying these non-hypocretin-1 deficient hypersomnolence forms. In some people with narcolepsy type 2 (but not in idiopathic hypersomnia), there have been reports of moderate loss of hypothalamic hypocretin-1 cells, while CSF-derived hypocretin-1 levels remain close to normal [32–34]. It is hypothesized that hypocretin-1 levels in CSF (derived through lumbar punctures) lack the sensitivity needed to detect such partial loss of hypocretin-1 neurons [35]. Partial hypocretin-1 neuron loss may therefore remain unnoticed in narcolepsy type 2. This suggests similar pathophysiological mechanisms in narcolepsy type 2 as observed in narcolepsy type 1 which should be further studied. The limited group sizes of narcolepsy type 2 and idiopathic hypersomnia preclude statistical subgroup comparisons but both diagnoses contributed similarly to the reported EBV, and other respiratory and non-respiratory infections. Flu was less frequently reported compared to narcolepsy type 1 which contrasts the hypothesis of similar underlying pathophysiologies. Molecular mimicry studies in narcolepsy type 2 and idiopathic hypersomnia between pathogens underlying the reported infections and hypocretin-1 neurons and other neuron systems involved in sleep-wake regulation should be performed. These studies could provide important new pathophysiological insights in the relationship between infections and onset of narcolepsy type 2 and idiopathic hypersomnia. Previous reports described that some people positive for HLA-DQB1*0602 are initially diagnosed with narcolepsy type 2 and, because of occult or still evolving hypocretin-1 deficiency, at a later stage develop cataplexy [29,36,37]. HLA-DQB1*0602 positivity was surprisingly common (80%) in our sample of people with narcolepsy type 2. The underlying pathophysiology of the transition to narcolepsy type 1 remains unknown but it could align with the multiple-hit hypothesis [1]. In our study we identified six people (all positive for HLA-DQB1*0602) who had EDS and reported an infection just before developing cataplexy. These individuals would have first been classified as narcolepsy type 2 or idiopathic hypersomnia because of the initial absence of cataplexy if hypocretin-1 levels were not measured at first presentation. This suggests that secondary immunological triggers could play an important role in this transitioning process of people diagnosed as narcolepsy type 2. Our small sample of people with narcolepsy type 2 does not allow for direct statistical comparisons with the narcolepsy type 1 group on potential trigger distributions. Future studies should include larger samples of people with narcolepsy type 2 with longer follow-up to test whether those who later develop cataplexy initially report similar potential triggers to those directly diagnosed with narcolepsy type 1.

The different potential trigger distribution suggests differences in potential triggers between narcolepsy type 1 and narcolepsy type 2 and idiopathic hypersomnia. EBV was particularly commonly reported in narcolepsy type 2 and idiopathic hypersomnia. One small study found positive EBV serology in people with idiopathic hypersomnia [30], but no direct link has yet been reported on symptomatic EBV infection before the onset of a central disorder of hypersomnolence. Multiple subjects across all central hypersomnolence disorders reported having symptomatic EBV infection just before onset of their sleep disorder. Symptomatic EBV infection is known to cause complaints of fatigue, pharyngitis, tonsillitis, fever, and cervical lymphadenopathy [38]. Fatigue could be mistaken for expressing a central disorder of hypersomnolence leading to a test bias. Long-lasting EBV symptoms are rare but have been described and may include EDS [39,40]. EDS complaints (and cataplexy in narcolepsy type 1) were continuously present in our study for multiple years in people who reported EBV infection. EBV has been associated with the onset of other (presumed) autoimmune disorders, including multiple sclerosis and multiple haematological malignancies [41–43]. A potential role for EBV in triggering hypersomnolence should be further assessed.

2009–2010H1N1 influenza vaccination was commonly reported as a trigger in people with narcolepsy type 1. No relationship was seen for influenza vaccination in other years. Influenza vaccinations have consistently included H1N1 since 2009. Pandemrix employed a novel adjuvant (AS03) that elicited a potentiated immune response, hypothesized as the primary factor for developing narcolepsy type 1 [44]. Discontinuation of this adjuvant after 2010 could explain why we found no association between influenza vaccination and narcolepsy type 1 onset outside 2009–2010. Multiple influenza vaccine brands were administered in the Netherlands during 2009–2010. Eight individuals with narcolepsy type 1 said they had received Pandemrix and two Focetria. Without a national vaccination registry, we could not trace the type of vaccination in other individuals. All children from six months to five years old and people living in their households, paediatric at-risk populations, soldiers on foreign deployments and pregnant women were offered 2009–2010H1N1 influenza vaccination with Pandemrix in

the Netherlands [45]. Eleven children in our sample between six months and five years old were reported to have received H1N1 influenza vaccination. More than one-year latency between H1N1 influenza vaccination and narcolepsy type 1 symptom onset was frequently seen and is in line with previous reports in the United Kingdom [28]. Our sample's latency was up to ten years, making a direct relationship unlikely. Why Pandemrix could have resulted in rapid onset of narcolepsy type 1 in some but not in others remains unknown. These others have possibly experienced additional triggers closer to narcolepsy type 1 onset. Other vaccinations unrelated to influenza were also reported before narcolepsy type 1 onset and included HPV, hepatitis A and hepatitis B vaccination. Routine HPV vaccination has only recently been introduced and is normally administered around the same age as when narcolepsy symptoms generally arise. Previous studies have also not found increased narcolepsy incidence rates following HPV vaccination [46,47], so this finding should not be over-interpreted.

Several participants in our study who received an H1N1 influenza vaccination also reported an infection directly linked to the onset of their narcolepsy type 1. It remains unclear why immunological events rapidly trigger the onset of hypersomnolence symptoms in some, whereas, in others who experienced the same trigger, narcolepsy symptoms take many years to arise in individuals with delayed onset. It could be that the initial trigger induced a slow-paced autoimmune process that remained asymptomatic at first, or that additional triggers, closer to symptom onset or in different environmental circumstances, were needed to trigger the onset of the hypersomnolence disorder. This idea aligns with the multiple-hit model in which people with a specific genetic predisposition must experience multiple environmental triggers to develop narcolepsy [1]. In our sample, flu and other respiratory infections were frequently associated with the rapid development of narcolepsy type 1 with short delays between EDS and cataplexy. This suggests that these infections are relatively strong triggers for developing narcolepsy type 1 in genetically susceptible people. Longer delays between EDS and cataplexy were generally seen after EBV infection, implying that it is a weaker potential trigger. This aligns with a recent genome-wide association study (GWAS) that suggests that genetic polymorphisms in narcolepsy type 1 lead to increased influenza viral uptake by dendritic cells and antigen presentation to $CD4^+$ T-cells [48]. This strong immune response to influenza infection could play a crucial role in the autoimmune attack leading to hypocretin deficiency. Interestingly, no genetic associations were found related to bacterial infection clearance. The genetic relationship between respiratory infections (such as streptococcus pyogenes) and narcolepsy type 1 development remains unclear.

The higher prevalence of infections in people with narcolepsy type 2 and idiopathic hypersomnolence than in people with narcolepsy type 1, should not be overinterpreted. In people with EDS without cataplexy, physicians are more likely to check the medical history to rule out other potential causes for excessive sleepiness, potentially leading to increased identification of preceding infections. In many people with narcolepsy type 2 or idiopathic hypersomnia, the reported infections occurred long before onset of their hypersomnolence disorders. This was seen less in narcolepsy type 1. In cases where no infection was identified in narcolepsy type 2 and idiopathic hypersomnia, we believe the opposite may be true, leading to an overestimation of infection prevalence in these diagnoses. As narcolepsy type 2 and idiopathic hypersomnia had so far not been associated with immunological triggers, we think that physicians could have been more prone to not document absence of an infection compared to presence of an infection. This could explain why missing reports of possible infections were also more often seen in narcolepsy type 2 and idiopathic hypersomnia (57.4%) compared to narcolepsy type 1 (46.5%). To overcome this issue, we have also included analyses on the distribution of reported immunological events to identify whether different types of potential triggers were relatively more prevalent in both groups.

4.1. Study limitations

The absence of a control group of healthy individuals makes it difficult to conclude whether infection and influenza vaccination rates were higher than expected from similarly aged controls or people with other (neurological) disorders. In a large French study [5], the overall incidence rates of EBV, streptococcal, upper respiratory tract and gastrointestinal infections, and non-H1N1 influenza vaccinations were similar in people with narcolepsy with cataplexy and controls. The study reported that infectious episodes were common in both groups but did not provide data on the timing of these infections concerning the onset of narcolepsy symptoms. Our goal was not to identify whether infections or influenza vaccinations were more common in people with a hypersomnolence disorder. Instead, we performed detailed analyses on the timing of reported potential triggers concerning the onset of the central disorder of hypersomnolence. We additionally identified the diversity in immunological events that people reported before developing their hypersomnolence disorder and tested whether this distribution differed between narcolepsy type 1 and non-hypocretin-1 deficient diagnoses. An important limitation of our study is the substantial percentage of individuals with missing infection/influenza vaccination histories. This has impacted our sample sizes. Especially in narcolepsy type 2 and idiopathic hypersomnia the limited sample size hindered us to further compare reported immunological events between these non-hypocretin-1 deficient groups. Future international collaborations are necessary to replicate our findings in larger samples of narcolepsy type 2 and idiopathic hypersomnia, and advance our comprehension of these elusive conditions.

Unnoticed infections due to no or mild symptoms are very common, and this could have resulted in underestimations of the absolute prevalences of infectious triggers. We however believe that unnoticed infections have introduced limited bias in our results as there is no reason to expect that one of the groups has a higher or lower chance to develop unnoticed infections. We also compared distributions of potential trigger types between the hypersomnolence groups (and not absolute prevalences). Many of the reported infections in our study may be triggered by multiple bacteria and viruses, and the exact pathogens responsible for the infections reported in this study often remain unknown. Symptoms caused by influenza infection for instance substantially overlap with respiratory syncytial virus (RSV), and influenza infection could also manifest with non-respiratory symptoms [49]. We therefore decided to report clinical diagnoses instead of underlying pathogens. EBV infections were the exception as they were generally verified using serology. Future studies should aim to use polymerase chain reaction (PCR) instead of serology for EBV detection as it identifies explicitly ongoing EBV infections [50]. The retrospective nature and self-reports of infection and vaccination history are limitations of this study resulting in possible recall bias. It is often difficult to recall precise timing of the EDS onset for people with a central disorder of hypersomnolence, especially in absence of cataplexy. People are also likely to remember events occurring close to life-changing events (such as hypersomnolence disorder onset). The symptom onset and infection and vaccination histories were generally documented during the semi-structured intake interview, and medical history was also checked through available correspondence with other healthcare providers such as the general practitioner. We hereby included as detailed information as possible in our analyses to limit the possible effects of recall bias. By including all people with a central disorder of hypersomnolence who visited our clinic between 2010 and 2020 we have also taken out possible selection bias effects despite being a specialized sleep-wake clinic. Our analyses included people with an ICSD-3 complaint and a clinical diagnosis. In Appendix B, we repeated the analyses excluding those with a clinical diagnosis and found highly comparable results.

5. Conclusions

Our results have identified various immunological events related to narcolepsy type 1 onset, including H1N1 influenza vaccinations, flu, and other respiratory and non-respiratory infections. A different distribution of immunological events with relatively more EBV, other respiratory and non-respiratory infections was seen in narcolepsy type 2 and idiopathic hypersomnia. Infections and influenza vaccinations were often reported within days to weeks of hypersomnolence symptom onset, making a causal relationship plausible. Our study opens a new research path into possible immunological pathophysiology underlying non-hypocretin-1 deficient central hypersomnolence diagnoses, including EBV and other respiratory infections.

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Statement of significance

H1N1 flu infections, streptococcal infections, and Pandemrix H1N1 vaccinations have been reported as potential triggers for developing narcolepsy type 1. Our large-scale real-world sample investigated all immunological events reported before developing narcolepsy type 1, type 2 and idiopathic hypersomnia. A wide variety of potential immunological events was found, significantly different between hypersomnolence subtypes. Events were often reported shortly before disease onset. Our study provides an opportunity to develop new hypotheses on the onset of immune-mediated narcolepsy type 1, in which other (influenza) viruses and immunological events should also be considered. We also suggest a potential role for infections, including EBV and other non-flu respiratory infections, in triggering development of narcolepsy type 2 and idiopathic hypersomnia.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

CRediT authorship contribution statement

Jari K. Gool: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zhongxing Zhang:** Writing – review & editing, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rolf Fronczek:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Pauline Amesz:** Writing – review & editing, Data curation, Conceptualization. **Ramin Khatami:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Gert Jan Lammers:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Lammers GJ reports a relationship with Alkermes plc that includes: consulting or advisory. Lammers GJ reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory. Lammers GJ reports a relationship with Bioprojet that includes: consulting or advisory. Lammers GJ reports a relationship with Jazz Pharmaceuticals plc that includes: consulting or advisory. Fronczek R reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory. Fronczek R reports a relationship with Bioprojet that includes: consulting or advisory, funding grants, and speaking and lecture fees. Fronczek R reports a relationship with Jazz Pharmaceuticals plc that includes: funding grants. Khatami R reports a relationship with Neuraxpharm that includes: consulting or advisory. Khatami R reports a relationship with Idorsia Pharmaceuticals Ltd that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2024.02.033.

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