




Red Flags for early referral of people with symptoms suggestive of narcolepsy: a report from a national multidisciplinary panel

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Abstract

Objective Narcolepsy is a lifelong disease, manifesting with excessive daytime sleepiness and cataplexy, arising between childhood and young adulthood. The diagnosis is typically made after a long delay that burdens the disease severity. The aim of the project, promoted by the “Associazione Italiana Narcolettici e Ipersonni” is to develop *Red Flags* to detect symptoms for early referral, targeting non-sleep medicine specialists, general practitioners, and pediatricians.

Materials and methods A multidisciplinary panel, including patients, public institutions, and representatives of national scientific societies of specialties possibly involved in the diagnostic process of suspected narcolepsy, was convened. The project was accomplished in three phases. Phase 1: Sleep experts shaped clinical pictures of narcolepsy in pediatric and adult patients. On the basis of these pictures, *Red Flags* were drafted. Phase 2: Representatives of the scientific societies and patients filled in a form to identify barriers to the diagnosis of narcolepsy. Phase 3: The panel produced suggestions for the implementation of *Red Flags*.

This manuscript is dedicated to the memory of Icilio Ceretelli (15.04.1948- 07.11.2018), founder of the Italian Narcolepsy Association (AIN). He deeply wanted and promoted this project and hardly worked for its fulfillment.

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Promoted by: the Italian association of patients with narcolepsy and hypersomnia (Associazione Italiana Narcolettici e Ipersonni, AIN). The following scientific societies and institutions endorsed the project by appointing a representative member: the Italian society of neurology (Società Italiana di Neurologia, SIN); the Italian society of pediatric neurology (Società Italiana Neurologia Pediatrica, SINP); the Italian society of social and preventive medicine (Società Italiana di Pediatria Preventiva e Sociale, SIPPSS); the Italian society of pediatrics (Società Italiana di Pediatria, SIP); the Italian society of general practitioners (Società Italiana di Medicina Generale, SIMG); the Italian society of neuropsychiatrists for children and adolescents (Società italiana di neuropsichiatria dell'infanzia e dell'adolescenza, SIMPIA); the World Association of Sleep Medicine (WASM); the Italian association of sleep medicine (Associazione Italiana Medicina del Sonno, AIMS), the Italian association of healthcare managers (Associazione Nazionale Medici di Direzione Ospedaliera), the Italian institute of health (Istituto Superiore di Sanità, ISS).

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Results *Red Flags* were produced representing three clinical pictures of narcolepsy in pediatric patients ((1) usual sleep symptoms, (2) unusual sleep symptoms, (3) endocrinological signs) and two in adult patients ((1) usual sleep symptoms, (2) unusual sleep symptoms). Inadequate knowledge of symptoms at onset by medical doctors turned out to be the main reported barrier to diagnosis.

Conclusions This report will hopefully enhance knowledge and awareness of narcolepsy among non-specialists in sleep medicine in order to reduce the diagnostic delay that burdens patients in Italy. Similar initiatives could be promoted across Europe.

Keywords Narcolepsy · Cataplexy · Diagnostic delay · Red flags · Diagnostic criteria · Burden of disease

Introduction

Narcolepsy is characterized by the pentad of excessive daytime sleepiness, cataplexy, hypnagogic or hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep [1–3]. It is a chronic and disabling disorder, with a bimodal peak for age at onset, with a maximal rate of onset at 15 years and the second peak at 35 years, needing a lifelong treatment [4].

Narcolepsy has a prevalence between 20 and 50 per 100,000 [5–11] and is recognized as rare disease (RF 0150) by the Italian Ministry of Health [attachment 1 at DM N. 279/2001]. At December 31, 2014, 610 patients were recorded in Italy by the National Registry for Rare Diseases [12], with an average national annual incidence in the 3-year period 2012–2014 of 0.97 per 1 million person-years [13] compared to an annual incidence of 1.37 per 100,000 person-years in Olmsted County, Minnesota (USA) [7].

The current classification [1] distinguishes narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2). Both types feature daytime sleepiness confirmed by polysomnographic studies, while hypocretin level of less than 110 pg/mL and the presence of cataplexy characterize only NT1. Therefore, NT1 is linked to the loss of hypothalamic hypocretinergic neurons, while the cause of NT2 remains unknown. Both genetic and environmental factors play a crucial role in the pathogenesis of narcolepsy. Most patients with narcolepsy carry HLA-DQB1*0602 and a link to polymorphisms in other non-HLA genes that may affect immune regulatory function and to several infectious triggers, supporting an autoimmune pathogenesis [2, 3].

Although narcolepsy has an early onset, a diagnostic delay that often exceeds 10 years from symptoms onset is reported [14–18]. Lately, there has been a trend toward a shorter diagnostic delay, which could potentially be attributed to an increased awareness of narcolepsy, as for example in Italy through media campaigns [<https://www.narcolessia.org>]. However, as emerged from a recent survey conducted by the Italian association of patients with narcolepsy and hypersomnia (Associazione Italiana Narcolettici e Ipersonni – AIN; <https://www.narcolessia.org>), diagnostic delay continues to be an issue, which makes identifying its causes a priority.

Data from several studies and reviews suggest that the primary reason for diagnostic delay is likely the lack of symptoms recognition, often resulting in misdiagnosis [14–16, 18–22]. This may originate from several factors, including lack of recognition, on the part of the clinician, of the signs and symptoms of narcolepsy, leading to multiple referrals before receiving a proper diagnosis [14, 20–22] as well as misdiagnosis of narcolepsy as another condition, such as epilepsy, depression, or attention-deficit/hyperactivity disorder, which further delays treatment [14, 19, 20, 23, 24].

Receiving a correct narcolepsy diagnosis is especially relevant in children, in order to timely face consequences, such as low academic achievement and social difficulties [18]. This is an important pitfall to be addressed, as misdiagnosis is more common in pediatric narcolepsy [19, 20, 25]. Indeed, the strongest predictor of a delayed diagnosis, along with the absence of cataplexy, has been reported to be pediatric onset of symptoms [26]. Diagnosis of narcolepsy indeed may be particularly challenging in children as symptoms may manifest differently from adults. Excessive daytime sleepiness can manifest as attentional problems, paradoxical hyperactivity, elongation of nighttime sleep, and resuming of postprandial sleep [3]. Hallucinations can be underrecognized because of the difficulty for children to recognize and describe them and for the possible coexistence of nightmares, rapid eye movement (REM) sleep behavior disorder (RBD), sleep terrors, and confusional arousals [26, 27]. Children with NT1 may have peculiar features of cataplexy with subcontinuous hypotonia, mainly involving the facial district “cataplectic face” and superimposed dyskinesia [23, 24, 28].

Timely diagnosis means better outcomes and it has been reported that patients diagnosed before age 30 years exhibit lower unemployment rates and have better health perception than those diagnosed at a later age [29], therefore resulting in reduced psychological distress along with socioeconomic and healthcare consequences [30–34]. Accordingly, it is important to understand the reason of this pitfall in diagnosis and to act in order to correct this gap and improve the rate of a timely diagnosis.

Considering these premises and the result of the above-mentioned AIN survey, AIN itself has promoted this

document with the specific aim of exploring, at multiple levels of the healthcare system, the causes of diagnostic pitfalls and of proposing corrective actions. We propose of doing this through *Red Flags* aimed at detecting narcolepsy symptoms early and timely referring potentially affected individuals to specialist care.

Objective

The aim of the project is to develop *Red Flags* to improve the knowledge about the symptoms suggestive of narcolepsy among non-sleep medicine expert physicians potentially involved in the first referral of patients (neurologists, pediatric neurologists, general practitioners, and pediatricians) for early referral to sleep medicine centers. The focus is the definition of the exemplary (*chief complaint*) and atypical (*variant complaint*) clinical presentations of narcolepsy, at its onset or when fully developed, in children and in adults. The analysis of barriers and facilitators of the diagnostic suspicion of narcolepsy was carried out with the aim of suggesting strategies for the implementation of the *Red Flags*.

Methods

The current document is a position paper, promoted by AIN, based on experts' and stakeholders' opinions. The following scientific societies endorsed the project by appointing a representative member of each society: the Italian society of neurology (Società Italiana di Neurologia, SIN; P. C.); the Italian society of pediatric neurology (Società Italiana Neurologia Pediatrica, SINP; V. M.); the Italian society of social and preventive medicine (Società Italiana di Pediatria Preventiva e Sociale, SIPPS; M.C. V.); the Italian society of pediatrics (Società Italiana di Pediatria, SIP; E. V.); the Italian society of general practitioners (Società Italiana di Medicina Generale, SIMG; M. B.); the Italian society of neuropsychiatrists for children and adolescents (Società italiana di neuropsichiatria dell'infanzia e dell'adolescenza, SIMPIA; R. G., F. M.); the World Association of Sleep Medicine (WASM; L. F-S.); the Italian association of sleep medicine (Associazione Italiana Medicina del Sonno, AIMS; R. F.), the Italian association of healthcare managers (Associazione Nazionale Medici di Direzione Ospedaliera; ANMDO; G. P.). A scientific committee was established, including a patients' representative (I. C., AIN), methodology experts from IRCCS Istituto delle Neuroscienze di Bologna (L. V.) and Italian institute of health - National Centre for Rare Diseases (Istituto Superiore di Sanità, ISS: C. C., D. T.), and narcolepsy experts (E. A., F. P., F. I., L. F-S., R. F. and G. P.).

The document was planned at an initial meeting of the scientific committee and scientific societies spokespersons in

Bologna (Italy), July 21, 2017. Three phases were conceived: (1) *Red Flags* editing; (2) barriers and facilitators analysis; (3) suggestions for *Red Flags* implementation.

Red Flags editing

Based on the AASM ICSD 3 [1] criteria for narcolepsy and by consulting evidence-based summaries [35–37], sleep experts defined the exemplary and atypical clinical pictures of narcolepsy, at onset or fully developed, in children and in adults. In particular, each *Red Flag* was edited as a short statement including the alerting symptom(s), either according to the possible chief complaints or the possible variant complaints. An explanation box, reporting examples of real-life presentation of symptoms, equipped each *Red Flag*. For each piece of evidence at the basis of the statement, the possible references labeled with their study design were reported. A first draft was submitted to the whole members group and a final consensus version was achieved. *Red Flags* were edited in Italian then translated into English (See [Supplementary Material](#)).

Barriers and facilitators analysis

An electronic questionnaire was built to investigate barriers and facilitators of the diagnostic suspicion of narcolepsy. The questionnaire was designed according to the “Tailored Implementation for Chronic Diseases” (TICD) checklist [38], a comprehensive tool that identifies determinants, that is barriers and facilitators, of healthcare professional practice. Briefly, it includes 57 potential determinants of practice, grouped in seven domains (guideline factors; individual health professional factors; patient factors; professional interactions; incentives and resources; capacity for organizational change; and social, political, and legal factors). The scientific committee chose the relevant domains and determinants conceivably involved in the diagnostic process of patients with suspicion of narcolepsy. Each determinant was transformed as question with a 4-point Likert scale (possible answers: “strongly agree,” “agree,” “disagree,” “strongly disagree”). The checklist was then edited in three versions and submitted to the scientific societies spokespersons, child patient caregivers, and adult patients. Patients and caregivers were invited by AIN.

Suggestions for Red Flags implementation

A list of suggestions aiming at the implementation of the *Red Flags*, based on the results of the Phase 2 analysis, was edited by the whole group during a final meeting.

Table 1 Explanation of pediatric patients *Red Flag 1* on excessive daytime sleepiness. This *Red Flag* was formulated based on core literature consisting of the international diagnostic criteria [1], one evidence-based clinical summary [36], three reviews [3, 39, 40], one cohort study [24], one incidence cross-sectional study [41], one case report [42]

In pediatric patients **excessive daytime sleepiness** may present with:

- ... **sleep attacks**, occurring in unusual and non-monotonous conditions, usually of brief duration, with a refreshing effect and with the recall of vivid dreams
- .. **change (acute or progressive) of sleep-wake circadian rhythm** with the tendency to increase the total sleep hours per day, to resume the habitual napping that occurs beyond the age when a child typically grows out of the need for daily naps (i.e. after five to six years of age), to go to sleep earlier and to wake up later and with major difficulties in the morning awakening
- ... onset during daytime of **hyperactivity, inattention, irritability and automatic behaviors**. Those symptoms are more easily observable at school, as for example the child progressively starts writing with a shoddy handwriting or with incomprehensible spelling until interrupting completely the handwriting

It should be kept in mind that in children the most frequent differential diagnoses of these symptoms are chronic sleep deprivation, psychological problems, seizures, infectious encephalopathies. Therefore, if one or more of these conditions are suspected, narcolepsy should also be considered in the differential diagnosis.

Table 2 Explanation of pediatric patients *Red Flag 1* on cataplexy. This *Red Flag* was formulated based on core literature consisting of the international diagnostic criteria [1], one evidence-based clinical summary [36], one review [3], one cohort study [24], two case-series [23, 28], two case reports [43, 44]

In pediatric patients **cataplexy** may present with:

- ... brief (seconds-minutes) episodes of **loss of muscle tone** triggered by emotions, during wakefulness. The loss of muscle tone can be partial (eyelid ptosis, mouth opening, tongue protrusion, head drop, slurred speech, trunk drop) and/or generalized (up to fall to the ground)
- ... **cataplectic face, droopy expression**, with the nearly constant but fluctuating presence of eyelid ptosis, mouth opening, tongue protrusion. Cataplectic face may be present sub-continuously with intermittent exacerbation due to daily life activities (i.e. eating, playing or being involved in an activity with emotional involvement, as playing with videogames, watching a funny movie, etc.)
- ... **floppy aspect**, that may involve mainly the head and the trunk (with intermittent episodes of head and trunk drops) or all the body and the legs appearing limply with a wobbly, wide-based, unstable, ataxic-like gait
- **intermittent active movements**, mainly involving the face (grimacing, eyebrow raising, perioral dyskinesias, tongue thrusting movements, tongue protrusion) or the body (stereotypies and choreic-like movements)

It should be kept in mind that in pediatric patients the most frequent differential diagnoses of these symptoms are neuromuscular disorders and hyperkinetic movement disorders. Therefore, if such conditions are suspected, narcolepsy should also be considered in the differential diagnosis. The fluctuating character (not triggered by exercise) and the association with excessive daytime sleepiness may help in differential diagnosis.

Results

Red Flags were produced representing three clinical pictures of narcolepsy in children (picture with (1) usual sleep symptoms, (2) unusual sleep symptoms, (3) metabolic symptoms) and two in adults (picture with (1) usual sleep symptoms, (2) unusual sleep symptoms). See [Supplementary Material](#) for original version in Italian.

Red flags for pediatric patients

Narcolepsy should be suspected in pediatric patients that present with...

1. **Excessive daytime sleepiness and/or cataplexy** (see Tables 1 and Table 2 for explanations).

→ *In this case, it is recommended that the patient should be referred to the reference centers for the diagnosis.*

2. **peculiar sleep-related disorders, i.e., hypnagogic-hypnopompic hallucination, sleep paralysis, and impaired nocturnal sleep** (see Table 3 for explanations).

→ *In this case, it is recommended that the presence of excessive daytime sleepiness and cataplexy (as indicated in Red Flag 1) should be investigated, even if these symptoms are not directly reported by the patient. In case of positive history of excessive daytime sleepiness and/or cataplexy, it is recommended that the patient should be referred to the reference centers for the diagnosis*

Table 3 Explanation of pediatric patients *Red Flag 2* on peculiar sleep-related disorders. This *Red Flag* was formulated based on core literature consisting of the international diagnostic criteria [1], one evidence-based clinical summary [36], two reviews [3, 45], four case-series [46–49]

In pediatric patients **peculiar sleep-related disorders** may present with:

- Multimodal **hallucinations** (mainly visual) or illusions that appear at sleep onset (hypnagogic) or on awakening (hypnopompic)
- **Vivid dreams**, mainly with frightening contents
- **Sleep paralyzes**, i.e. inability to move for one or two minutes immediately after awakening or just before falling asleep, accompanied by a disquieting sensation with or without concomitant hallucinations/illusions
- **Impaired nocturnal sleep**, with agitations, fragmented sleep and **REM sleep behavior disorder (RBD)**, i.e. with the presence of movements that mimic the dream content (enacted dreams) (i.e. the patient moves as if he/she were acting what he/she is dreaming; upon awakening he/she recalls a vivid dream coherent with the performed movements)

It should be kept in mind that in pediatric patients in the full-blown disorder, these symptoms are usually accompanied by excessive daytime sleepiness and cataplexy. It is rare, but possible, that these symptoms represent the initial manifestations of the disease. In children, given the low insight and the embarrassment in reporting unpleasant or embarrassing experiences, these are rarely reported spontaneously and difficult to investigate.

Table 4 Explanation pediatric patients Red Flag 3 on endocrinological signs. This *Red Flag* was formulated based on core literature consisting of the international diagnostic criteria [1], one evidence-based clinical summary [36], one review [3], one cohort study with controls [50], one retrospective cohort study [51], one cross-sectional study with controls, [52], one case-series [53]

In children, near to the onset, narcolepsy can be accompanied by **endocrinological signs**, i.e. acceleration/anticipation of pubertal signs until reaching criteria for precocious puberty and the progressive increase of weight until reaching the criteria for obesity. In these conditions therefore, it is recommended that the symptoms of narcolepsy should be investigated as reported in *Red Flags 1 e 2*.

- signs of **precocious puberty** and/or increase of weight until the development of **obesity** (see Table 4 for explanations).

→ *In this case, it is recommended that the presence of excessive daytime sleepiness and cataplexy (as indicated in Red Flag 1) should be investigated, even if these symptoms are not directly reported by the patient. In case of positive history of excessive daytime sleepiness and/or cataplexy, it is recommended that the patient should be referred to the reference centers for the diagnosis.*

Red flags for adult patients

Narcolepsy should be suspected in adult patients that present with ...

- Excessive daytime sleepiness and/or cataplexy** (see Tables 5 and 6 for explanations).

→ *In this case, it is recommended that the patient should be referred to the reference centers for the diagnosis.*

- peculiar **sleep-related disorder, i.e., hypnagogic-hypnopompic hallucination, sleep paralysis, and impaired nocturnal** (see Table 7 for explanations).

→ *In this case, it is recommended that the presence of excessive daytime sleepiness and cataplexy (as indicated in Red Flag 1) should be investigated, even if these symptoms are not directly reported by the patient. In case of positive history of excessive daytime sleepiness and/or cataplexy, it is recommended that the patient should be referred to the reference centers for the diagnosis.*

Barriers and facilitators analysis

The following domains and determinants were selected from the TICD checklist to design and to analyze questionnaire

Table 5 Explanation of adult patients *Red Flag 1* on excessive daytime sleepiness. Red Flag 1 on excessive daytime sleepiness was formulated based on core literature consisting of the international diagnostic criteria [1], two evidence-based clinical summaries [35, 37], one review [2]

In adult patients **excessive daytime sleepiness** may present with:

- ... **sleep attacks**, occurring in unusual and non-monotonous conditions, usually of brief duration, with a refreshing effect and with the recall of vivid dreams
- ... **change (acute or progressive) of sleep-wake circadian rhythm** with the tendency to increase the total sleep hours per day and to be prone to fall asleep throughout the day, often at inappropriate times

It should be kept in mind that in adults the most frequent differential diagnoses for these symptoms are obstructive sleep apnea, chronic sleep deprivation, psychological problems, and seizures. Therefore, if one or more of these conditions are suspected, narcolepsy should also be considered in the differential diagnosis.

results: (a) individual health professional factors (knowledge and skills; cognition and attitudes; professional behavior); (b) patient factors (needs; beliefs and knowledge; preferences; motivation; behavior); (c) professional interactions (referral processes); (d) incentives and resources (nonfinancial incentives and disincentives; assistance for clinicians); (e) capacity for organizational change (regulations, rules policies); (f) social, political, and legal factors (legislation).

Scientific societies spokespersons

Five specialist spokespersons completed the survey (a general practitioner, a neurologist, a child neuropsychiatrist, a child neurologist, a general pediatrician).

For most specialists, main barriers of diagnostic suspicion of narcolepsy are the insufficient knowledge of symptoms at onset, and the insufficient skill or propensity to examine symptoms when they are considered atypical (elongation of 24-h sleep, hallucinations, cataplexy,

Table 6 Explanation of adult patients *Red Flag 1* on cataplexy. This *Red Flag* was formulated based on core literature consisting of the international diagnostic criteria [1], two evidence-based clinical summaries [35, 37], one review [2], three case-series [54–56].

In adult patients **cataplexy** may present with:

- ... brief (seconds-minutes) episodes of **loss of muscle tone** triggered by emotions, during wakefulness. The loss of muscle tone can be partial (eyelid ptosis, mouth opening, tongue protrusion, head drop, slurred speech, trunk drop) and/or generalized (up to fall to the ground)
- ... transient episodes (seconds-minutes) with **speech and action arrest** without a clear hypotonia, but always with retained consciousness.

It should be kept in mind that in adult patients the most frequent differential diagnoses of these symptoms are seizures and cerebrovascular attacks. Therefore, if such conditions are suspected, narcolepsy should also be considered in the differential diagnosis. The absence of an aura and the integrity of consciousness in narcolepsy may help in the differential diagnosis.

Table 7 Explanation of adult patients *Red Flag 2* on peculiar sleep-related disorders. This *Red Flag* was formulated based on core literature consisting of the international diagnostic criteria [1], two evidence-based clinical summaries [35, 37], three reviews [2, 57, 58], two case-series [59, 60]

In adult patients **peculiar sleep-related disorders** may present with:

- Multimodal **hallucinations** (mainly visual) or illusions which present at sleep onset (hypnagogic) or on awakening (hypnopompic)
- **Sleep paralyzes**, i.e. inability to move for one or two minutes immediately after awakening or just before falling asleep, accompanied by a disquieting sensation with or without concomitant hallucinations/illusions
- **Impaired nocturnal sleep**, with agitations, fragmented sleep and **REM sleep behavior disorder (RBD)**, i.e. with the presence of movements that mimic the dream content (enacted dreams) (i.e. the patient moves as if he/she were acting what he/she is dreaming; upon awakening he/she recalls a vivid dream coherent with the performed movements)

It should be kept in mind that in adult patients these symptoms may occur as isolated phenomena, such as for example isolated idiopathic RBD or RBD in neurodegenerative conditions. However, in presence of one or more of these conditions, the co-occurrence of excessive daytime sleepiness and of cataplexy should also be investigated.

nighttime sleep disruption with rapid eye movement (REM) sleep behavior disorder, sleep terrors) or when they are reported as disease consequences (attentional problems, paradoxical hyperactivity, worsening of school or work performances). Another barrier is represented by the difficult referral process to expert sleep centers, due to the geographical distance or the difficulty of booking an appointment. Social or legal factors are not deemed as a relevant cause of the diagnostic delay; however, the fear

of losing the driving license was raised by one specialist as a possible diagnostic barrier. Possible facilitators are tools to elicit the diagnostic suspicion or to improve the knowledge (questionnaires and educational materials, both printed and on the web; toll-free number) and organizational changes to simplify the access to expert sleep centers (dedicated outpatients' clinic; diagnostic–therapeutic pathway).

Pediatric patients

Twenty-three caregivers of pediatric patients (14 males/9 females) completed the survey; narcolepsy type 1 was the prevalent diagnosis (21). The sample was quite homogeneously distributed in the Italian areas (north west 39%; north east 14%; middle 30%; south and islands 17%). Median age at onset was 9 years, and mean diagnostic delay 2.1 years (SD 3.5; median 1; range 0–14). Narcolepsy was not suspected at the first visit in 61% of patients; 47% of them consulted more than two physicians, and up to 10 in one case. Reported alternative diagnoses (in 48% of patients) are other organic disorders (epilepsy, obstructive sleep apnea syndrome, brain neoplasm, iron deficiency, drug abuse, tics, precocious puberty), psychological problems, abnormal attitudes/behaviors (boredom, laziness).

Main barrier to the diagnostic suspicion of narcolepsy was the inadequate knowledge of the disease by physicians (see Table 8). Relevant was also the scarce awareness of symptoms in their child by parents. To be noticed, the presence of more

Table 8 Main barriers of diagnostic suspicion of narcolepsy according to caregivers of pediatric patients and adult patients

Determinants (domain and specific determinant)	Judged as relevant (% out of 23 pediatric patients' caregivers)	Judged as relevant (% out of 48 adult patients)
Patient factors (beliefs and knowledge; behavior)		
Scarce awareness of symptoms by parents/patients	61%	64%
Individual health professional factors (knowledge and skills)		
Insufficient knowledge of the disease	79%	69%
Professional interactions (referral processes)		
Difficult access to expert sleep center	26%	23%
Social, political, and legal factors		
Social factors or legislation as barriers of the healthcare process	4%	34%
Barriers of diagnostic suspicion (open question)		
Insufficient knowledge of the disease by the physician	46%	55%
No awareness of symptoms by parents/patients	13%	12%
More popular competing disorders	8%	11%
Prejudices/social barriers	8%	8%
No knowledge of specialist centers	–	2%
None/no response	25%	12%

popular competing disorders (see above) among the possible barriers to diagnostic suspicion.

Adult patients

Forty-eight adult patients (25 males/23 females) completed the survey; narcolepsy type 1 was the prevalent diagnosis (32). The sample was quite homogeneously distributed in the Italian areas (north west 26%; north east 22%; middle 22%; south and islands 30%). Median age at onset was 11 years, mean diagnostic delay 6.7 years (SD 7.3; median 3.5; range 0–42). Narcolepsy was not suspected at first visit in 67% of patients; 59% of them consulted more than two physicians, and up to 10 in three cases. Reported alternative diagnoses (in 48% of patients) included other organic disorders (42%: epilepsy, obstructive sleep apnea syndrome, restless leg syndrome, gastroesophageal reflux, post-viral syndrome, obesity) and psychiatric disorders (43%: depression, anxiety), abnormal attitudes/behaviors (15%: laziness, tiredness).

Main barrier to the diagnostic suspicion of narcolepsy is the insufficient knowledge of the disease by physicians (see Table 8) and the scarce awareness of symptoms by patients. To be noticed, the presence of more popular competing disorders among the possible barriers to diagnostic suspicion. The presence of social/legislation factors (not acceptance of the disease, fear of social and work limitations, fear of driving license loss) is also reported as relevant by 1/3 of patients.

Suggestions for Red Flags implementation

After the analysis of the above reported data, the multidisciplinary panel agreed on the following suggestions to implement the above reported *Red Flags*.

- The *Red Flags* should be the object of a national campaign, with presentation at national congresses and meetings and publications in Italian journals targeted to the specialties relevant to the project.
- The *Red Flags* should be disseminated with simple educational materials, such as leaflets with cartoons or as web movies that can be distributed in primary care centers, or at school, where symptoms can be firstly recognized.
- To facilitate the access to the reference centers, in collaboration with the National Helpline on Rare Diseases (Telefono Verde Malattie Rare 800 89 69 49) of the Istituto Superiore di Sanità (National Centre for Rare Diseases), a national central call-center could be designed in order to drive and help clinicians in referring the patients to the nearest and more appropriate center.
- The recognition of the symptoms by physicians could be elicited by validated questionnaires. Due to the scarcity of

these tools in the Italian language (e.g., [61, 62] considering only excessive daytime sleepiness), a tool including the whole *Red Flags* should be devised and validated.

- The efficacy of the *Red Flags* implementation in reducing the diagnostic gap of patients with narcolepsy could be the object of a national multi-center study (e.g., an interrupted time series study).
- Similar initiatives could be promoted across European countries.

Discussion

Narcolepsy is still a disease burdened by an unacceptable diagnostic delay [18, 26] and possibly by missed diagnoses in Italy [12, 13].

The persistence of a substantial delay in recognizing symptoms of narcolepsy, even among sleep medicine specialists, has been highlighted also by the Awareness and Knowledge of Narcolepsy (AWAKEN) study [21]. This is a survey including a sample of 1000 US adults, 300 primary care physicians (PCPs), and 100 sleep medicine specialists conducted in the USA. The study showed that even if 62% of sleep specialists and 24% of PCPs considered themselves “very” or “extremely” knowledgeable about narcolepsy, only 42% and 9% of sleep specialists and PCPs, respectively, felt “very” or “extremely” comfortable diagnosing the disorder. The striking finding was however that only 22% of sleep specialists and 7% of PCPs identified all 5 key narcolepsy symptoms; particularly, while excessive daytime sleepiness and cataplexy were more easily recognized, the other symptoms were instead more rarely investigated and recognized.

An Italian survey disclosed that pediatricians and child neuropsychiatrists scored low in all areas of sleep knowledge and particularly in questions about narcolepsy, sleep apnea, and parasomnias [63].

In order to reach patients’ needs and overcome the diagnostic gap, AIN has promoted the initiative at issue aiming at analyzing the reasons that hamper a timely diagnosis and to offer to general clinicians, pediatricians, and neurologists a document containing *Red Flags* that can help in a prompt recognition of symptoms that can lead to suspect narcolepsy, in order to refer the patient to the reference centers for the diagnosis.

As far as barriers analysis is concerned, results of questionnaires confirmed that both patients and clinicians judged lack of knowledge of symptoms as a main factor hampering a right and timely diagnosis. Particularly, as emerged also in the AWAKEN study [21], the scarce knowledge about symptoms different from excessive daytime sleepiness and cataplexy

emerges as one of the main causes in delaying the proper recognition of the disease.

Indeed, in more than 60% of both pediatric and adult patients, narcolepsy was not suspected at the first outpatient evaluation; and therefore nearly 60% of patients needed to consult more than two physicians. In over 50% of cases, a diagnosis of different organic conditions (epilepsy, sleep apnea, brain lesions) or of a psychiatric condition was made.

Noteworthy, what came to light from our survey was the shorter mean diagnostic delay in Italy compared to other European data (namely 2.1 years for pediatric cases and 6.7 years for adults). This could be due to the shortening of the delay in the last years (note the difference between children and adults), also thanks to awareness campaigns on narcolepsy that AIN has been promoting since 2000. These data could also be biased by the small sample size and the recruitment process (voluntary).

Considering the differences in phenotypic presentations in adults and children, different sets of *Red Flags* have been produced for the two populations and we distinguished two different scenarios: the first one with symptoms that are already sufficient to suspect the diagnosis and two additional conditions for children and one for adults that concern associated symptoms in which we recommend instead to investigate the presence of excessive daytime sleepiness and cataplexy, prior referring patients to the reference centers for the diagnosis.

The panel focused particularly in defining the peculiar features of narcolepsy in children and mainly the discrete manifestation of excessive daytime sleepiness, which not always presents with sleep attacks and the typical phenotype of cataplexy in children.

Indeed, the best predictor of a delayed diagnosis, along with the absence of cataplexy, is known to be the pediatric onset of symptoms [26]. This is because pediatric narcolepsy near the onset of the disease may have peculiar features [3, 36], as excessive daytime sleepiness may be manifested as paradoxical hyperactivity, elongation of nighttime sleep, resume of post prandial sleep and symptoms like hallucinations, RBD, and confusional arousals may be difficult to be articulated by children [26, 27]. Similarly, cataplexy at onset may present with the peculiar subcontinuous hypotonia and “cataplectic face” with superimposed dyskinesia or motor hyperactivity resembling other neurodevelopmental disorders [23, 24, 28].

Experts also focused on the description of symptoms different from excessive daytime sleepiness and cataplexy, since both the AWAKEN survey [21] and our own survey highlighted that clinicians may be more confident in investigating the cardinal features of narcolepsy (i.e., excessive daytime sleepiness and cataplexy), while less so in identifying the remaining symptoms typical of the narcolepsy pentad, i.e., hallucinations, sleep paralysis, and disrupted nocturnal sleep with RBD.

This report, by producing *Red Flags* guiding in suspecting the diagnosis of narcolepsy, has been therefore an attempt to overcome the major barriers identified through the survey.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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References

1. American Academy of Sleep Medicine (2005) *The International Classification of Sleep Disorders: Diagnostic & Coding Manual*. 2nd ed. Rochester, MN: American Academy of Sleep Medicine
2. Scammell TE (2015) Narcolepsy. *N Engl J Med* 373:2654–2662
3. Postiglione E, Antelmi E, Pizza F, Lecendreux M, Dauvilliers Y, Plazzi G (2018) The clinical spectrum of childhood narcolepsy. *Sleep Med Rev* 38:70–85
4. Dauvilliers Y, Montplaisir J, Molinari N, Carlander B, Ondze B, Besset A, Billiard M (2001) Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology* 57:2029–2033
5. Hublin C, Partinen M, Kaprio J, Koskenvuo M, Guilleminault C (1994) Epidemiology of narcolepsy. *Sleep* 17:S7–12
6. Ohayon MM, Priest RG, Zulle J, Smirne S, Paiva T (2002) Prevalence of narcolepsy symptomatology and diagnosis in the European general population. *Neurology* 58:1826–1833
7. Silber MH, Krahn LE, Olson EJ, Pankratz VS (2002) The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. *Sleep* 25:197–202
8. Wing YK, Li RH, Lam CW, Ho CK, Fong SY, Leung T (2002) The prevalence of narcolepsy among Chinese in Hong Kong. *Ann Neurol* 51:578–584
9. Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G (2007) The epidemiology of narcolepsy. *Sleep* 30:13–26
10. Shin YK, Yoon IY, Han EK, No YM, Hong MC, Yun YD, Jung BK, Chung SH, Choi JB, Cyn JG, Lee YJ, Hong SC (2008) Prevalence of narcolepsy-cataplexy in Korean adolescents. *Acta Neurol Scand* 117:273–278
11. Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, Svanström H, Mølgaard-Nielsen D, Heijbel H, Dahlström LA, Hallgren J, Sparen P, Jennum P, Mosseveld M, Schuemie M, van der Maas N, Partinen M, Romio S, Trotta F, Santuccio C, Menna A, Plazzi G, Moghadam KK, Ferro S, Lammers GJ, Overeem S, Johansen K, Kramarz P, Bonhoeffer J, Sturkenboom MCJM (2013) The incidence of narcolepsy in Europe: before, during, and

- after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. *Vaccine* 31:1246–1254
12. Taruscio D, Rocchetti A, Torreri P, Ferrari G, Kodra Y, Salerno P, Vittozzi L (2017). Il Registro Nazionale Malattie Rare nel contesto nazionale e internazionale. 3° Rapporto (dati al 31 dicembre 2014). Roma: Istituto Superiore di Sanità. (Rapporti ISTISAN 17/8)
 13. Taruscio D, Vittozzi L, Rocchetti A, Torreri P, Ferrari L (2018) The occurrence of 275 rare diseases and 47 rare disease groups in Italy. Results from the National Registry of Rare Diseases. *Int J Environ Res Public Health* 15:1470
 14. Kryger MH, Walid R, Manfreda J (2002) Diagnoses received by narcolepsy patients in the year prior to diagnosis by a sleep specialist. *Sleep* 25:36e41
 15. Morrish E, King MA, Smith IE, Shneerson JM (2004) Factors associated with a delay in the diagnosis of narcolepsy. *Sleep Med* 5:37–41
 16. Thorpy MJ, Krieger AC (2014) Delayed diagnosis of narcolepsy: characterization and impact. *Sleep* 15:502–507
 17. Taddei RN, Werth E, Poryazova R, Baumann CR, Valko PO (2016) Diagnostic delay in narcolepsy type 1: combining the patients' and the doctors' perspectives. *J Sleep Res* 25:709–715
 18. Thorpy MJ, Hiller G (2017) The medical and economic burden of narcolepsy: implications for managed care. *Am Health Drug Benefits* 10:233–241
 19. Macleod S, Ferrie C, Zuberi SM (2005) Symptoms of narcolepsy in children misinterpreted as epilepsy. *Epileptic Disord* 7:13–17
 20. Kauta SR, Marcus CL (2012) Cases of pediatric narcolepsy after misdiagnoses. *Pediatr Neurol* 47:362–365
 21. Rosenberg R, Kim AY (2014) The AWAKEN survey: knowledge of narcolepsy among physicians and the general population. *Postgrad Med* 26:78–86
 22. Carter LP, Acebo C, Kim A (2014) Patients' journeys to a narcolepsy diagnosis: a physician survey and retrospective chart review. *Postgrad Med* 126:216–224
 23. Plazzi G, Pizza F, Palaia V, Franceschini C, Poli F, Moghadam KK, Cortelli P, Nobili L, Bruni O, Dauvilliers Y, Lin L, Edwards MJ, Mignot E, Bhatia KP (2011) Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. *Brain* 134:3477–3489
 24. Pizza F, Franceschini C, Peltola H, Vandi S, Finotti E, Ingravallo F, Nobili L, Bruni O, Lin L, Edwards MJ, Partinen M, Dauvilliers Y, Mignot E, Bhatia KP, Plazzi G (2013) Clinical and polysomnographic course of childhood narcolepsy with cataplexy. *Brain* 136:3787–3795
 25. Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E (2010) Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. *Sleep* 33:1457–1464
 26. Maski K, Steinhart E, Williams D, Scammell T, Flygare J, McCleary K, Gow M (2017) Listening to the patient voice in narcolepsy: diagnostic delay, disease burden, and treatment efficacy. *J Clin Sleep Med* 13:419–425
 27. Dunne L, Patel P, Maschauer EL, Morrison I, Riha RL (2016) Misdiagnosis of narcolepsy. *Sleep Breath* 20:1277–1284
 28. Serra L, Montagna P, Mignot E, Lugaresi E, Plazzi G (2008) Cataplexy features in childhood narcolepsy. *Mov Disord* 23:858–865
 29. Ingravallo F, Gnucchi V, Pizza F, Vignatelli L, Govi A, Dormi A, Pelotti S, Cicognani A, Dauvilliers Y, Plazzi G (2012) The burden of narcolepsy with cataplexy: how disease history and clinical features influence socio-economic outcomes. *Sleep Med* 13:1293–1300
 30. Dodel R, Peter H, Walbert T et al (2004) The socioeconomic impact of narcolepsy. *Sleep* 27:1123e8
 31. Smolensky MH, Di Milia L, Ohayon MM, et al (2011) Sleep disorders, medical conditions, and road accident risk. *Accid Anal Prev*; 43:533e48
 32. Jennum P, Ibsen R, Petersen ER et al (2012) Health, social, and economic consequences of narcolepsy: a controlled national study evaluating the societal effect on patients and their partners. *Sleep Med* 13:1086e93
 33. Ohayon MM (2013) Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. *Sleep Med* 14:488e92
 34. Ohayon MM, Black J, Lai C et al (2014) Increased mortality in narcolepsy. *Sleep* 37:439e44
 35. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 116132, Narcolepsy; [updated 2018 Mar 09, cited place cited date here]; [about 29 screens]. Available from <http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=116132>. Registration and login required. Last access May 28, 2018
 36. Kotagal S. Narcolepsy in children. Scammell TE, Chervin RD, Eichler AF, eds. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com>. Last access May 28, 2018
 37. Scammell TE. Clinical features and diagnosis of narcolepsy in adults. Benca R, Eichler AF, eds. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com>. Last access May 28, 2018
 38. Flottorp SA, Oxman AD, Krause J et al (2013) A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci* 23:8–35
 39. Wise J, Lynch J (2001) Narcolepsy in children. *Semin Pediatr Neurol* 8:198–206
 40. Babiker MO, Prasad M (2015) Narcolepsy in children: a diagnostic and management approach. *Pediatr Neurol* 52:557–565
 41. Partinen M, Saarenpää-Heikkilä O, Ilveskoski et al (2012) Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. *Plos One* 2:e33723
 42. Lee J, Na G, Joo EY, Lee M, Lee J (2017) Clinical and polysomnographic characteristics of excessive daytime sleepiness in children. *Sleep Breath* 21:967–974
 43. Prasad M, Setty G, Ponnusamy A et al (2014) Cataplectic facies: clinical marker in the diagnosis of childhood narcolepsy-report of two cases. *Pediatr Neurol* 51:517
 44. Dhondt K, Verhelst H, Pevernagie D, Slap F, Van Coster R (2009) Childhood narcolepsy with partial facial cataplexy: a diagnostic dilemma. *Sleep Med* 10:797–798
 45. Jardri R, Bartels-Velthuis DM et al (2014) From phenomenology to neurophysiological understanding of hallucinations in children and adolescents. *Schizophr Bull* 40:S221–S232
 46. Nevsimalova S, Prihodova I, Kemlink D, Lin L, Mignot E (2007) REM behavior disorder (RBD) can be one of the first symptoms of childhood narcolepsy. *Sleep Med* 8:784–786
 47. Lloyd R, Tippmann-Peikert M, Slocumb N, Kotagal S (2012) Characteristics of REM sleep behavior disorder in childhood. *J Clin Sleep Med* 8:127
 48. Pisko J, Pastorek L, Buskova J, Sonka K, Nevsimalova S (2014) Nightmares in narcolepsy: underinvestigated symptoms? *Sleep Med* 15:967–972
 49. Antelmi E, Pizza F, Vandi S, Neccia G, Ferri R, Bruni O, Filardi M, Cantalupo G, Liguori R, Plazzi G (2017) The spectrum of REM sleep-related episodes in children with type 1 narcolepsy. *Brain* 140:1669–1679
 50. Wang Z, Wu H, Stone WS, Zhuang J, Qiu L, Xu X, Wang Y, Zhao Z, Han F, Zhao Z (2016) Body weight and basal metabolic rate in childhood narcolepsy: a longitudinal study. *Sleep Med* 25:139–144
 51. Ponziani V, Gennari M, Pizza F, Balsamo A, Bernardi F, Plazzi G (2016) Growing up with type 1 narcolepsy: its anthropometric and endocrine features. *J Clin Sleep Med* 12:1649–1657

52. Poli F, Pizza F, Mignot E, Ferri R, Pagotto U, Taheri S, Finotti E, Bernardi F, Pirazzoli P, Cicognani A, Balsamo A, Nobili L, Bruni O, Plazzi G (2013) High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. *Sleep* 36:175–181
53. Dahmen N, Bierbrauer J, Kasten M (2001) Increased prevalence of obesity in narcoleptic patients and relatives. *Eur Arch Psychiatry Clin Neurosci* 251:85–89
54. Vetrugno R, D'Angelo R, Moghadam KK et al (2010) Behavioural and neurophysiological correlates of human cataplexy: a video-polygraphic study. *Clin Neurophysiol* 121:153–162
55. Overeem S, van Nues SJ, van der Zande WL, Donjacour CE, van Mierlo P, Lammers GJ (2011) The clinical features of cataplexy: a questionnaire study in narcolepsy patients with and without hypocretin-1 deficiency. *Sleep Med* 12(12):12–18
56. Pizza F, Antelmi E, Vandi S, Meletti S, Erro R, Baumann CR, Bhatia KP, Dauvilliers Y, Edwards MJ, Iranzo A, Overeem S, Tinazzi M, Liguori R, Plazzi G (2018) The distinguishing motor features of cataplexy: a study from video-recorded attacks. *Sleep* 41(5). <https://doi.org/10.1093/sleep/zsy026>
57. Plazzi G, Serra L, Ferri R (2008) Nocturnal aspects of narcolepsy with cataplexy. *Sleep Med Rev* 12:109–128
58. Dauvilliers Y, Jennum P, Plazzi G (2013) Rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia in narcolepsy. *Sleep Med* 14:775–781
59. Franceschini C, Ferri R, Pizza F, Ricotta L, Vandi S, Detto S, Poli F, Pruneti C, Mazzetti M, Cipolli C, Lugaresi E, Plazzi G (2011) Motor events during REM sleep in patients with narcolepsy-cataplexy: a video-polysomnographic pilot study. *Sleep Med* 12:S59–S63
60. Cipolli C, Franceschini C, Mattarozzi K, Mazzetti M, Plazzi G (2011) Overnight distribution and motor characteristics of REM sleep behaviour disorder episodes in patients with narcolepsy-cataplexy. *Sleep Med* 12:635–640
61. Rinaldi R, Vignatelli L, D'Alessandro R et al (2001) Validation of symptoms related to excessive daytime sleepiness. *Neuroepidemiology* 20:248–256
62. Vignatelli L, Plazzi G, Barbato A, Ferini-Strambi L, Manni R, Pompei F, D'Alessandro R, GINSEN (Gruppo Italiano Narcolessia Studio Epidemiologico Nazionale (2003) Italian version of the Epworth sleepiness scale: external validity. *Neurol Sci* 23:295–300
63. Bruni O, Violani C, Luchetti A, Miano S, Verrillo E, Di Brina C, Valente D (2004) The sleep knowledge of pediatricians and child neuropsychiatrists. *Sleep and Hypnosis* 6:130–138

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