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► **To cite this version:**

Lisa Brunel, Enzo Brossaud, Julien Lioret, Antoine Jaffiol, Louison Vanderghote, et al.. Effectiveness of an intervention program on physical activity in children with narcolepsy type 1. 2023. hal-04685348

HAL Id: hal-04685348

<https://hal.science/hal-04685348>

Preprint submitted on 3 Sep 2024

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Effectiveness of an intervention program on physical activity in children with narcolepsy type 1.

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Highlights:

- More than half of the children with narcolepsy were physically active
- Those who engaged in leisure time physical activities showed higher quality of life
- Those with depression are particularly responsive to a physical activity program

Abstract

Objectives: Physical activity (PA) is recommended as part of the management of narcolepsy type 1 (NT1). This study aimed at 1) characterizing PA in children and adolescents treated for NT1 using objective and subjective measurements, 2) evaluating how PA is associated with NT1 symptoms and comorbidities, and 3) evaluating the effects of an Adapted Physical Activity (APA) program on PA and clinical characteristics.

Patients/Methods: Patients with NT1 from the National Reference Center of Narcolepsy (Lyon, France) were consecutively included in an APA intervention protocol. Narcolepsy symptoms and comorbidities were collected using standardized questionnaires and sustained attention was evaluated using the Bron-Lyon Attention Stability Test before and after the four-week APA intervention. PA was measured objectively using actigraphy throughout the study.

Results: Twenty-seven NT1 patients were included (median age 14.7 years [8.3-18.4], cataplexy 88.9%, obesity 37.0%). At baseline, 52.4% of the patients had satisfactory PA levels according to international recommendations. Patients with leisure-time PA (LTPA) showed higher quality of life than patients without. 45% of the patients increased PA during the intervention compared to baseline. These responsive patients had more depressive feelings and tended to have lower objective PA than non-responsive patients at baseline. No significant correlation was found between PA levels before and during the intervention and other clinical data.

Conclusions: Most children with NT1 showed satisfying PA levels despite their daytime sleepiness. LTPA engagement was associated with higher quality of life. An APA intervention could be effective in children with narcolepsy, especially for those with depressive feelings.

Key words: sleep; narcolepsy; actigraphy; physical activity; pediatrics; interventional study

1. Introduction

Narcolepsy is a rare neurological disorder characterized by excessive daytime sleepiness (EDS). Abnormal rapid eye movement (REM) sleep manifestations (cataplexy corresponding to the sudden loss of muscle tone triggered by emotions, hypnagogic hallucinations, and sleep paralysis) can also be found in patients with narcolepsy, as well as disturbed nocturnal sleep [1]. Narcolepsy with cataplexy (NC) is usually characterized by cerebrospinal fluid (CSF) hypocretin-1 levels ≤ 110 ng/mL and is also called narcolepsy type 1 (NT1) or hypocretin-deficient narcolepsy. The direct cause of NT1 is the loss of hypocretin neurons located in the lateral hypothalamus, a loss generally imputed to autoimmune mechanisms as suggested by the fact that the majority of patients with NC present the human leukocyte antigen (HLA) DQB1*06:02 genotype [2,3].

More than half of the patients with narcolepsy have a disease onset prior to the age of 18 years old [5]. NC in children is associated with many comorbidities impacting daily life, such as depression [5], attention deficit hyperactivity disorder (ADHD) symptoms [6], and obesity [7]. More than 50% of children with NC suffer from obesity [8] and 17% of them present a metabolic syndrome [9].

Symptomatic treatments can be prescribed for patients with narcolepsy to promote wakefulness, improve nighttime sleep quality, and decrease cataplexy [10]. As these pharmacological options are only partially effective, behavioral treatments such as taking regular naps and maintaining good sleep hygiene are recommended [11]. Nutritional advice is also provided to patients due to their metabolic problems [12].

The World Health Organization (WHO) assigns many positive health outcomes to physical activity (PA), including improvements in weight, sleep, and mood [13]. It recommends exercising at a moderate-to-vigorous intensity for at least an average of 30 minutes per day for

adults, and for at least an average of 60 minutes per day for children and adolescents. A study by Donnelly et al. [14] showed that a 10-month intervention consisting in 5 walking or jogging sessions per week (with an energy expenditure of at least 400kcal/session) reduced body mass index (BMI) in a group of overweight and obese young adults. Moreover, PA could improve sleep quality, as it was shown to be associated with reduced sleep fragmentation, shorter sleep onset latency, and longer total sleep time [15]. Furthermore, PA can be recommended as a behavioral treatment for depression. In a group of adults with treatment-resistant major depressive disorder, depression improved when pharmacological treatment was associated with a PA intervention consisting in walking for 30-45 minutes 5 times per week for 12 weeks [16]. Given that poor sleep, excessive weight, and mood disorders are major comorbidities of NT1, promoting PA among these patients might be an interesting therapeutic approach, especially in children.

Only two studies have investigated the link between PA and NT1 in the past. They revealed that among children and adolescents with narcolepsy, those who engaged in leisure time physical activity (LTPA) ≥ 2 hours per week had lower sleepiness and BMI, better sleep quality [17], and fewer depressive symptoms [5]. Although the aforementioned studies have shown promising results, their observational design did not allow for any conclusion to be drawn on the benefits of PA in NT1 patients. Interventional studies are thus needed to establish whether a causal relationship exists between PA and improvements in NT1 symptoms and comorbidities.

The aims of the present interventional study were (1) to characterize PA in children and adolescents treated for NT1 using objective and subjective measures, (2) to evaluate how PA is associated with NT1 symptoms and comorbidities in these children at baseline, and (3) to evaluate in these children the effects of an Adapted Physical Activity (APA) program on PA, as well as on NT1 symptoms and comorbidities.

2. Methods

2.1. Patients

In 2022, the *Hôpital Femme Mère Enfant* of the Lyon teaching hospital (*Hospices Civils de Lyon*, France) received a funding for the E-HÔP project which aimed at including APA in the routine medical care of patients suffering from chronic diseases. From April to September 2022, all patients with narcolepsy aged from 6 to 18 years followed up in the National Reference Center for Narcolepsy in the *Hôpital Femme Mère Enfant* were proposed to add an APA program in their usual medical care and to be included in the E-HÔP project regardless of their usual PA level.

2.2. Ethical considerations

Parents were informed about the use of the clinical data of their child for research purposes and those who were not opposed to it were included. The study was approved by the institutional ethics committee of the *Hospices Civils de Lyon* and by the French national data protection agency (*Commission Nationale de l'Informatique et des Libertés*, CNIL n° 23-5242).

2.3. Diagnostic criteria

The criteria for the diagnosis of idiopathic narcolepsy were (1) complaints of excessive daytime sleepiness for at least 3 months, (2) symptoms not better explained by other medical or psychiatric disorders, (3) absence of secondary narcolepsy, (4) presence or absence of cataplexy, and (5) mean sleep latency ≤ 8 min and ≥ 2 sleep onset REM periods (SOREMPs) on Multiple Sleep Latency Test (MSLT) including nocturnal PSG [1]. However, a recent study defined the MSLT criteria in childhood NT1 as a mean sleep latency ≤ 8.2 min or ≥ 2 SOREMPs on MSLT including nocturnal PSG [18]. HLA-DQB1*0602 genotyping as well as CSF hypocretin levels were measured in the majority of patients. We considered NT1 diagnosis

when CSF hypocretin levels < 110 ng/l [19] or if the patient presented with cataplexy and positive HLA-DQB1*0602 genotyping.

2.4. Procedure

Patients who accepted to take part in the program E-HÔP received an actigraph (ActiGraph wGT3X-BT) at home and were instructed to wear it continuously for 15 days before their appointment with the sleep specialist (visit 1, V1) and then to keep it throughout the 4-week program. They met with their sleep specialist and with an APA teacher twice, at V1 and at the end of the intervention (visit 2, V2). During the two visits, the patients and their parents filled the questionnaires and performed the Bron-Lyon Attention Stability Test (BLAST). They were also examined by the physician who took anthropometric measures. At V1, the APA teacher gathered information about their activities in everyday life and recommended a customized training program. Patients were advised to follow it for four weeks, with at least one session per week. At the end of the four-week intervention (V2), the actigraph was returned (Figure 1).

2.5. Questionnaires

The patients completed five questionnaires and their parents filled out two questionnaires.

2.5.1. Patient questionnaires

Daytime sleepiness was assessed by an adapted version of the Epworth Sleepiness Scale for children and adolescents [20] validated in French (FSSA) [21]. A score above 11 is considered pathological for patients with narcolepsy.

The pediatric version of the Narcolepsy Severity Scale (NSS-P) was used to evaluate the main symptoms of the disease [23], as usually done in their follow-up examination. Scores ranging from 0-14 indicate mild symptoms, scores between 15-28 indicate moderate symptoms, scores between 29-42 indicate severe symptoms, and 43-54 indicate very severe symptoms. Items 8 and 9 of the NSS-P assess the frequency of cataplexy: partial cataplexy for item 8 and total

cataplexy for item 9, scored between 0-5. For each patient, the highest score among these items was considered a measure of the general frequency of cataplexy with 0 indicating the absence of cataplexy and higher scores the presence of cataplexy.

The Insomnia Severity Index (ISI) was used to evaluate the quality of nighttime sleep through 7 items scored from 0 to 4 [24]. A final score of 8-14 indicates mild insomnia while a score of 15-21 suggests moderate insomnia and scores above 21 indicate severe insomnia.

A psychological assessment of symptoms of depression was completed through the Children's Depression Inventory (CDI) [25]. The 27 items are scored from 0 to 2; final scores above 16 are considered pathological.

The patients' health related quality of life (HRQL) was evaluated, either through the *Vécu et Santé Perçue de l'Adolescent* (VSP-A) for adolescents or through its version adapted to children (*Vécu et Santé Perçue de l'Enfant*, VSP-E) if the patient was under 10 years old [26,27]. Scores between 0 and 100 were computed for each of the following dimensions, independently: psychological and physical well-being, leisure, vitality, body image, parents and family, friends, medical staff, teachers, school performance. Adolescents had an additional dimension about social and sexual life. A global score was computed by averaging scores from all the dimensions for which at least 50% of the items were answered. A higher HRQL score indicates a higher quality of life. In this study, we gathered global scores from VSP-A and VSP-E to constitute a single HRQL variable for the sample: VSP-A/E.

2.5.2. Parent questionnaires

The patients' parents also completed an HRQL questionnaire according to their perception of their child's quality of life. The parent version of the VSP (VSP-P) is a 49-item questionnaire scored similarly to the VSP-A and VSP-E [28,29]. Higher scores indicate a higher quality of life, as perceived by parents.

The 48-item Conners' Parent Rating Scale (CPRS-48) [30] was used to assess behavioral and attention disorders. This scale is divided into six components (conduct, learning, psychosomatic, impulsivity, anxiety, and hyperactivity), the scores of which are standardized according to age groups. Moderate to severe symptoms are defined with a cut-off above 65 and severe symptoms are defined with a cut-off above 75.

2.6. Bron-Lyon Attention Stability Test (BLAST)

The BLAST [31] was taken on a tactile tablet. Subjects were instructed to repeatedly detect the presence or absence of a target letter in an array of four letters. The target letter was displayed at the center of the screen for 200 milliseconds (ms), followed by a mask for 500 ms, followed by an array of four letters displayed until an answer was given. If the target letter was in the array of letters, the participants had to answer "yes" by tapping the tablet using their non-dominant hand. If the target letter was absent from the array, they had to answer "no" by tapping the screen using their dominant hand. The next trial started with the presentation of a new target letter 800 ms after the previous response if the previous trial answer was correct, and 4800 ms after if the previous trial answer was incorrect. There were fifty trials in total and the exact duration of the test depended on speed and accuracy. To evaluate attention, four behavioral measures of the BLAST were selected: error rate (%), median reaction time (RT, ms), BLAST-Stability, and BLAST-Intensity. BLAST-Stability reflects the ability to give successive correct answers with regular RT, and BLAST-Intensity is the ability to give successive correct answers with fast RT. For both BLAST-Stability and BLAST-Intensity, higher scores correspond to better performances. Results were compared to normative data from more than 6000 participants aged between 8 to 70 years [31].

2.7. Medical examination and anthropometric measurements

Weight (in kg) and height (in cm) were collected through a medical examination performed by a sleep specialist at V1 and V2. BMI z-score was computed as a measure of weight adjusted for height, sex, and age relative to a smoothed reference distribution [32]. Obesity was determined using the International Obesity Task Force curves of BMI [33]. Diagnosis, age at diagnosis, and treatments were collected from the medical files.

2.8. Evaluation of physical activity

Some information about lifestyle was self-reported during the meeting with the APA teacher at V1 while PA was continuously recorded using an actigraph for 6 weeks (2 weeks before the intervention and 4 weeks during the intervention).

2.8.1. Subjective physical activity

On the day of the first appointment at the hospital, the APA teacher collected information about weekly LTPA (in hours, h) and daily screen time (in h). A four-week PA program was recommended by the APA teacher based on the information collected about the patients' needs, preferences, and abilities.

2.8.2. Objective physical activity

PA was objectively recorded throughout the protocol via actigraph monitoring using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, FL), a 3-axis accelerometer worn by the patients at the waist. The amount of motor activity was collected and stored in 1-minute epochs. Data were processed using the software ActiLife 6 (ActiGraph, Pensacola, FL). Days when the device had been worn less than 70% of the time (i.e. <1008 minutes/day) were excluded from the analyses. To measure PA, the vector magnitude (VM, in counts per minute, CPM) of the three axes of the accelerometer was used to calculate an activity count. Using the VM, each 1-minute epoch was assigned a level of intensity. In order to compare the PA data obtained to

normative data, the same cut-points were used [34]: PA was either considered light ($VM \leq 2295$ CPM), moderate (VM in range 2296 – 4012 CPM), or vigorous (≥ 5280 CPM). Time spent in moderate-to-vigorous PA (MVPA, in minutes) and mean VM (in CPM) were calculated for each day, one day being considered from 7 am to 6:59 pm to exclude nocturnal activity [34]. MVPA was used to compare the sample to the WHO recommendation to engage in at least an average of 60 minutes of MVPA per day. School and days off (weekends and school holidays) were both considered for the analyses.

2.9. APA intervention

The training sessions proposed within the APA intervention were customized for each patient based on the information gathered during the V1 interview. Thereafter, each week during a phone interview, the APA teacher made adjustments to the training sessions if necessary. A training session involved 5 different aerobic and muscle-strengthening exercises, which were repeated 4 times. A typical training session is provided in Supplementary materials (Table S1). The patient took a 45-second break between two exercises and a 90-second break before repeating the 5 exercises.

2.10. Statistical Analyses

Statistical analyses were conducted using RStudio, version 4.2.3 [35]. Continuous variables are expressed as median [range] and discrete variables as count (percentage).

2.10.1. PA before the intervention (V1)

We first conducted a descriptive analysis of the data collected prior to the APA intervention. Self-reported screen time was compared between school days and days off using a paired Wilcoxon test (R-stats package). A square-root transformation was applied to VM data at baseline (V1) to correct the distribution of the model residuals. At V1, the effects of the type of day (school day vs day off) and of screen time (≤ 2 h/day vs > 2 h/day, according to the WHO

definition of sedentary lifestyle [36]) on VM were tested using a type II variance analysis (R-car package version 3.1.1 [37]) applied to a linear model with participant as random effect (R-lme4 package [38]).

Spearman correlations (R-stats package) were used to explore the relationships between objective PA (MVPA, VM), age, BMI, and clinical parameters (questionnaires, BLAST). LTPA was considered as a binary variable in the analyses: unpaired Wilcoxon test (R-stats package) was used to compare quality of life of patients engaged or not in LTPA (LTPA = 0h/week vs LTPA > 0h/week).

2.10.2. Effects of the intervention (V2)

As the distribution of the model residuals was different when V1 and V2 data were pooled together compared to V1 only (2.10.1), a log-transformation was applied to the VM data collected throughout the protocol (V1 + V2) to correct the distribution of the new model residuals. Effect of the period (V1 vs V2) on VM was tested using a type II variance analysis applied on a linear model with participant as random effect. The sample was then split into two groups: “responsive” (patients whose mean VM difference between V1 and V2 was greater than 0) and “non-responsive” (patients whose mean VM difference between V1 and V2 was negative or null). Anthropometric, clinical, and PA data at V1 were compared between the two groups using unpaired Wilcoxon tests (R-stats) and Fisher’s exact tests (R-stats). Unpaired Wilcoxon tests (R-stats) were also used to compare the percentage of evolution of the clinical parameters (BMI, questionnaires, and BLAST) from V1 to V2 between the two groups (“responsive” vs “non-responsive”). Finally, clinical symptoms were compared in the “responsive” group between V1 and V2 using paired Wilcoxon tests (R-stats) and Fisher’s exact tests (R-stats).

The significance level was set at $p = 0.05$. Asterisks (*) mark p-values of the results that remain significant after Bonferroni correction ($p < 0.0005$).

3 Results

3.1 Patient characteristics

Twenty-seven patients with NT1 (13 females, 14 males) were included in the program, all with cataplexy at diagnosis. MSLT at diagnosis showed 4 [0 – 4] SOREMPs and a median sleep latency of 2.2 minutes [0.4 – 13.9]. Four patients did not meet the adult diagnostic MSLT criteria for narcolepsy (median age = 13.1 years [8.3 – 17.5]), 1 of whom did not present with at least 2 SOREMPs. However, they all met the children's MSLT criteria and were thus kept in the analysis.

HLA-DQB1*0602 genotyping was performed in 25 patients (92.6%) and was positive for 24 (96.0%) of them. CSF hypocretin levels were measured in 24 patients (88.9%) and were below 110pg/mL for all of them. The 3 patients for whom hypocretin levels were unknown reported experiencing regular cataplexies and had positive HLA-DQB1*0602 genotyping.

3.2 Clinical and physical activity data before the intervention

3.2.1 Clinical profile

At V1, the median [range] age of the included children was 14.7 years [8.3-18.4], 24 presented with cataplexy (88.9%) and 10 with obesity (37.0%; Table 1). All patients were on stable treatment for narcolepsy symptoms (Table S2). Table 2 presents the results from the questionnaires and the BLAST at V1. Despite treatment, daytime sleepiness was above pathological threshold in 20 patients (74.1%). Narcolepsy severity was moderate for 19 patients (76.0%) and severe for 3 patients (12.0%). Depressive symptoms were found in 6 patients (24.0%) and moderate insomnia in 5 patients (20.8%). Conners F6 scores evoked hyperactivity

for 2 patients (7.7%). One BLAST was excluded because the error rate was higher than 50%, which was considered chance level. A second BLAST was excluded because it was completed on a day when usual medication had not been taken by the patient. The patients' performance on the BLAST are represented in comparison with normative data in Supplementary materials (Figure S1). Median error rate was 4% [0-10]. Median RT was longer than average for 19 patients (76.0%), however BLAST-Stability and BLAST-Intensity were above the average for 19 patients (76.0%).

3.2.2 *Physical activity patterns*

In total, we gathered actigraphic recordings from 4 to 14 days before the intervention and from 5 to 30 days during the intervention.

Before the intervention, 51.9% of the children reported being engaged in LTPA and 75.0% exceeded the WHO recommended limitation for daily screen use of ≤ 2 h/day (Table 3). Objective PA data were obtained from 21 of the 27 patients, and no significant difference in terms of age and BMI z-score was found between the total cohort and those for whom actigraphic recordings were obtained. According to the objective PA data, 52.4% of the patients followed the WHO recommendation of at least an average of 60 min of MVPA per day (Table 3).

The objective PA data were then compared to normative data from Steene-Johannessen et al. (2020) [34], according to age and sex. MVPA was equal or higher than the 50th percentile for 12 patients (57.1%) whereas VM was equal or higher than the 50th percentile for 9 patients (42.9%) (Figure 2).

VM variability at V1 was partly explained by the type of day (school days vs days off; Wald $\chi^2 = 18.755$, $df = 1$, $p < 0.0001^*$), median VM being higher on school days (530.9 CPM [192.9 – 976.0] on school days vs 369.8 CPM [145.3 – 831.0] on days off). Median screen time was

higher on days off compared to school days (4.0 h/day [1 – 10] on days off vs 1.5 h/day [0 – 5.5] on school days; $p < 0.01$; Table S3). There was no significant interaction of type of day and screen time (≤ 2 h/day vs > 2 h/day) on VM variability.

3.2.3 Links between physical activity and clinical profile

Age and MVPA recorded before the intervention were negatively correlated to one another ($p = 0.03$, $R^2 = -0.5$). Quality of life (assessed by VSP-A/E with scores out of 100) was significantly higher in patients who engaged in LTPA (65.3 [48.3 – 92.6] with LTPA vs 54.7 [31.6 – 76.3] without LTPA, $p = 0.04$). No other significant association was found between PA (LTPA, VM, MVPA) and clinical profiles.

3.3 Effects of APA intervention

3.3.1 Effects on physical activity

Objective PA data were collected before and after the intervention for 20 patients. The period (before vs during intervention) significantly explained the VM variability (Wald $\chi^2 = 21.085$, $df = 1$, $p < 0.00001^*$), median VM being higher during the intervention compared to before (509.5 CPM [215.5 – 1656.3] during the intervention vs 454.3 CPM [165.2 – 905.3] before the intervention; Table S4).

Nine patients (45.0%) increased their VM during the intervention (Figure 3), with a median increase of 58.6% (215.9 CPM). Comparisons of anthropometric measures, objective and subjective PA, questionnaires and BLAST performance at V1 between the responsive and non-responsive groups are provided in Table 4. At V1, patients in the responsive group showed a higher median CDI score (17.5 [2 – 22] in the responsive group vs 9.5 [2 – 15] in the non-responsive group; $p = 0.04$), and a higher proportion of pathological CDI scores (62.5% in the responsive group vs 0% in the non-responsive group; $p < 0.01$). No other significant differences were observed at V1 between patients in the responsive vs non-responsive groups regarding

anthropometric measures, questionnaire scores, BLAST performance, subjective PA level (LTPA), and VM. However, the responsive group tended to have lower MVPA compared to patients in the non-responsive group (52.0 min/day [12.4 - 100.9] in the responsive group vs 71.6 min/day [31.0 - 138.1] in the non-responsive group; $p = 0.07$). At V1, PA levels were below the WHO recommendations for 66.7% of the responsive group and for 27.3% of the non-responsive group ($p = 0.2$). However, during the intervention, there were only 2 patients (22.2%) below the WHO recommendations in the responsive group.

3.3.2 Effects on narcolepsy symptoms and comorbidities

There was no significant difference between the responsive vs non-responsive groups in terms of percentage of evolution from V1 to V2 of the clinical parameters. There was no significant difference regarding anthropometric measures, questionnaires and BLAST performance between V1 and V2 in the responsive group (Table S5).

4 Discussion

The four-week APA intervention proposed in the present study led to an increase in PA for nearly half of the children with NT1 included, especially for those with low PA activities and depressive feelings.

4.1 Before APA intervention

The anthropometric and clinical characteristics of the present sample were consistent with those reported in the literature regarding pediatric narcolepsy. Obesity was in the range of the 20-50% prevalence previously reported in this population [5,6]. The frequency of depressive symptoms observed herein were also similar to previous reports [5,28]. The proportion of the sample affected by insomnia was also in line with the 25% incidence reported by Barateau et al. (2022) [23]. The Conners' scores indicated symptoms evocative of ADHD for 7.6% of the sample, which is lower than previously reported by Lecendreux et al. (2015) [39] in a group of

treated and untreated children with NC (15%) but still high compared to the incidence of ADHD reported in the general pediatric population (5 %) [40]. Despite being on treatment, 74.1% of the present sample still had a pathological sleepiness score and 12.0% had severe symptoms according to the NSS-P.

4.1.1 BLAST

In accordance with previous findings [41–43], the performances on the BLAST suggest that patients with NT1 have longer RTs than average. However, this slowness seems to allow correct accuracy and stability. Yet, according to the Instability State Theory [44], sleepiness induces fluctuations of attention during wake resulting in more variable RTs and attentional lapses. Such fluctuations of attention may however be reduced herein because of treatment, as a study reported that children with NT1 show better attentional capacity after the first year of treatment [45].

4.1.2 Physical activity

Interestingly, despite their disease, children herein did not seem to be limited to perform PA in school and extra-school settings. No patient was excused from physical education lessons at school and half of them reported being engaged in LTPA. Moreover, most of them had MVPA comparable or higher than healthy children and adolescents. Half of them were already applying the WHO recommendations prior to the intervention (i.e., MVPA for at least an average of 60 minutes per day) [36]. This might seem unexpected, given that narcolepsy reduces energy and vitality [28], and yet, previous studies are in line with these results. Filardi et al. (2018) [17] found that 60% of children with NT1 engaged in LTPA for at least 2 hours per week while Parmar et al. (2019) reported that 73.3% of children with narcolepsy were physically active [5]. Moreover, many adolescents and adults with narcolepsy report using PA as a behavioral therapy for sleepiness [11,46].

Although PA levels seem satisfactory in the present cohort, results show that three quarters of the children had a screen time that exceeded the WHO recommendations for daily screen time limitation. This high number is consistent with what is reported in the general pediatric population; Hysing et al. (2015) found an average screen use duration of about 6 hours/day for adolescents [47]. Longer screen use durations are associated with stronger nighttime sleep disruption [48] and sleepiness [49], which are issues already experienced by patients with narcolepsy [50]. Moreover, as has already been reported in the French pediatric population [51], the present results suggest that the daily amount of PA decreases with age, that PA levels are lower on days off than on school days, and that screen time is longer on days off.

The present findings also confirm that children with LTPA have a higher quality of life than those without [52], even when suffering from NT1. This might be explained by increased self-esteem [53] or an enhanced feeling of social integration [54]. Filardi et al. (2018) [17] had also found that LTPA was associated with lower daytime sleepiness, better sleep quality and metabolic parameters (such as HDL cholesterol), which the present study could not show, possibly because of a smaller sample size and the use of subjective tools to evaluate sleep quality (ISI) compared to Filardi et al. who relied on objective PSG data.

4.2 Effects of the APA intervention

Young patients with NT1 can be responsive to an APA intervention program as shown by the increase in objective PA in 45.0% of the sample. Support from APA teachers can help promote PA among patients not yet engaged in such activities. In fact, in the present sample, most of the patients for whom PA level increased during the program were not active enough at baseline according to the WHO recommendations. Moreover, all patients for whom CDI scores evoked depressive symptoms were responsive to the intervention, implying that an APA intervention may be an adequate motivation for them to exercise more.

In the general population, PA interventions have been shown to improve depression, obesity, and insomnia [14,16,55]. Herein, the increase in PA level during the intervention was not associated with improvements in NT1 symptoms and comorbidities. Numerous factors may be responsible for this, among which is the design of the intervention itself. The program was relatively short, lasting only 4 weeks, and the patients followed the program at home without direct supervision, with only one phone call per week from the APA teacher. Buman and King (2010) [56] proposed that, in order to change sleep quality, interventions should last at least 16 weeks and include sessions with PA intensity exceeding the general recommendations.

In addition, the use of an accelerometer to measure PA has some limitations, which may have led to an inaccurate assessment of PA levels. While its use is considered more reliable than subjective questionnaires to measure PA levels in adolescents [57], all activities cannot be monitored. For example, the device cannot be worn while swimming (as it is not waterproof) and the recording during activities such as bodybuilding and cycling is not accurate. Therefore, the amount of PA may have been underestimated for some patients. To overcome this, patients could be asked to log when they take the device off for specific activities. Moreover, the actigraphic data after 7 pm were excluded from the analyses in order to allow a comparison with the results from Steene-Johannesse et al. (2020) [34], which could exclude late PA sessions, even in young patients with narcolepsy.

By correcting p-values with the Bonferroni method, part of our results does not remain significant. For more robust conclusions, we suggest future protocols to include more patients and for a longer interventional period. The limited sample size of the present study is explained by the fact that NT1 is a rare disease; a multi-center study could help increase sample size.

5 Conclusions

In the present sample of young patients with NT1, higher LTPA was associated with higher quality of life. Despite excessive sleepiness, most patients were engaged in PA in respect to the WHO recommendations. An APA intervention could be effective in children with narcolepsy, especially for those with depressive feelings.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was supported by the French Sleep Research and Medicine Society (SFRMS). We especially acknowledge Verena Landel for her help in manuscript preparation.

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TABLES AND FIGURES

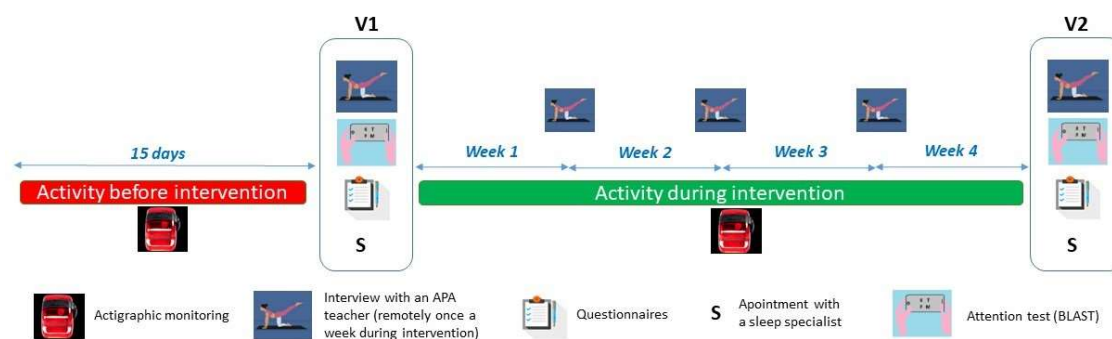


Figure 1 Experimental design

Abbreviations: APA, adapted physical activity; BLAST, Bron-Lyon attention stability test; V1, visit 1; V2, visit 2.

Table 1 Demographic, clinical, and anthropometric data at V1.

		n
Age (years)	14.7 [8.3 - 18.4]	
< 12	5 (18.5)	27
≥ 12	22 (81.5)	
Sex		
Female	13 (48.1)	27
Time since diagnosis (years)	4.5 [0.7 – 12.9]	27
Cataplexy	24 (88.9)	27
BMI z-score	2.4 [-0.5 – 10.1]	27
Obesity	10 (37.0)	27

Data are expressed as median [range] or n (%).

Abbreviation: BMI, body mass index.

Table 2 Questionnaire scores and performance on the BLAST at V1.

	Scores	n
Questionnaires		
FSSA score	13 [7 - 21]	
Pathological (> 11)	20 (74.1)	27
ISI score	10 [1 - 18]	
Moderate insomnia (15 – 21)	5 (20.8)	24
Severe insomnia (> 21)	0 (0)	

NSS-P score	19 [11 - 35]	
Moderate symptoms (15 – 28)	19 (76.0)	25
Severe symptoms (29 – 42)	3 (12.0)	
CDI score	10 [2 - 22]	
Pathological (> 16)	6 (24)	25
VSP-A/E score	58.5 [31.6 – 92.6]	26
VSP-P score	68.7 [31.8 – 93.4]	25
Conners F1 (conduct)	47 [38 - 84]	
Moderate symptoms (66 – 75)	1 (3.8)	26
Severe symptoms (> 75)	1 (3.8)	
Conners F2 (learning)	47 [36 - 68]	
Moderate symptoms (66 – 75)	2 (7.7)	26
Severe symptoms (> 75)	0 (0)	
Conners F3 (psychosomatic)	56 [42 - 104]	
Moderate symptoms (66 – 75)	3 (11.5)	26
Severe symptoms (> 75)	3 (11.5)	
Conners F4 (impulsivity)	44 [35 - 73]	
Moderate symptoms (66 – 75)	4 (15.4)	26
Severe symptoms (> 75)	0 (0)	
Conners F5 (anxiety)	44.5 [40 - 73]	
Moderate symptoms (66 – 75)	2 (7.7)	26
Severe symptoms (> 75)	0 (0)	
Conners F6 (hyperactivity)	47 [36 - 86]	
Moderate symptoms (66 – 75)	1 (3.8)	26
Severe symptoms (> 75)	1 (3.8)	
BLAST		
Error rate (%)	4 [0 - 10]	
Median RT (ms)	739 [491 – 1064]	
Longer than average	19 (76.0)	25
BLAST-Stability	35 [13 - 69]	
Lower than average	6 (24.0)	
BLAST-Intensity	65 [45 - 82]	
Lower than average	6 (24.0)	

Data are expressed as median [range] or n (%). FSSA assesses sleepiness, ISI insomnia, NSS-P narcolepsy severity, CDI depression, and VSP quality of life (VSP-A/E for patients; VSP-P for parents).

Table 3 PA data collected before the intervention.

		n
Subjective PA		
LTPA (h/week)	1 [0 – 6.5]	
0	13 (48.1)	27
]0 ;2[3 (11.1)	
≥ 2	11 (40.7)	
Screen time (h/day)	2.4 [0.9 – 6.2]	
≤ 2	6 (25.0)	24
]2 ;4[12 (50.0)	
≥ 4	6 (25.0)	
Objective PA		
VM (CPM)	443.3 [165.2 – 905.3]	
Female (n = 7)	520.4 [234.8 – 664.5]	21
Male (n = 14)	440.5 [165.2 – 905.3]	
MVPA (min/day)	60.9 [12.4 – 138.1]	
Female (n = 7)	63.1 [31.0 – 100.9]	21
Male (n = 14)	57.5 [12.4 - 138.1]	
≥ 60 min	11 (52.4)	

Data are expressed as median [range] or n (%).

Abbreviations: CPM, counts per minute; LTPA, leisure-time physical activity; MVPA, moderate-to-vigorous activity; VM, vector magnitude.

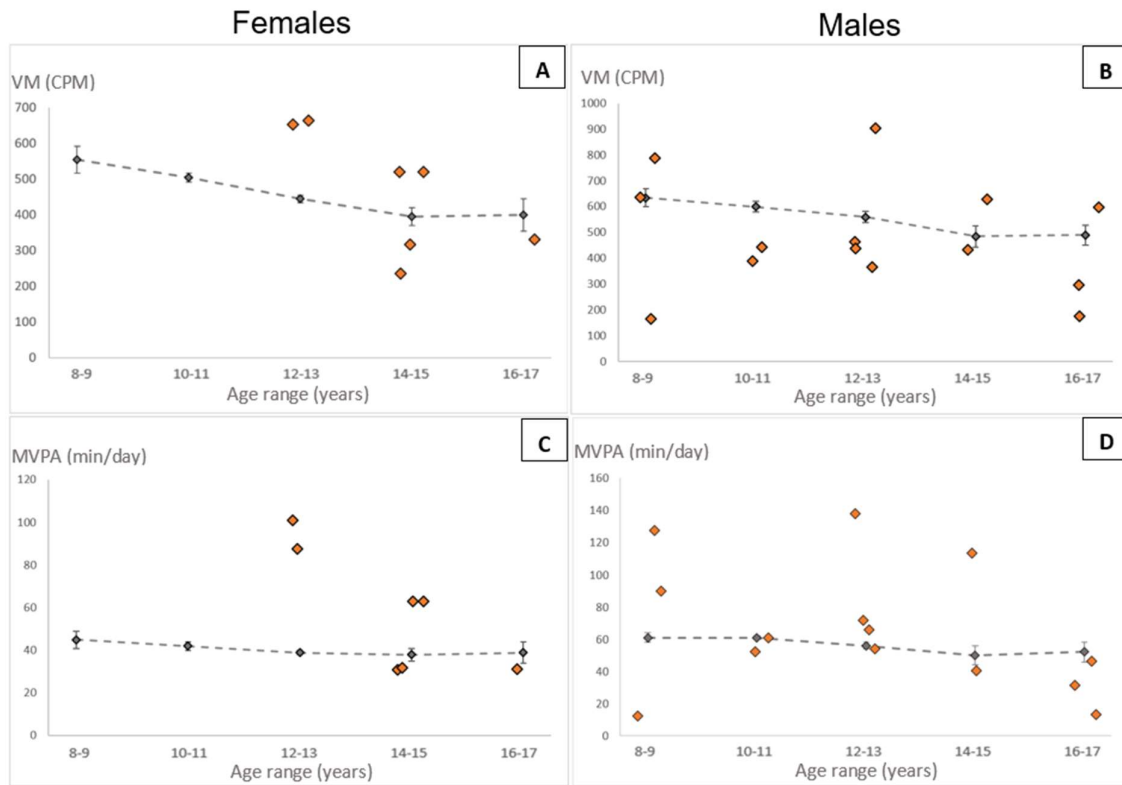


Figure 2 Objective PA data in 21 children with narcolepsy type 1 (7 females, 14 males) compared to normative data from Steene-Johannessen et al. (2020) according to age range and sex. (A) VM of females; (B) VM of males; (C) MVPA of females; (D) MVPA of males. Patients are represented as orange marks; normative data are represented as grey marks connected by dashed lines.

Abbreviations: CPM, counts per minute; MVPA, moderate-to-vigorous physical activity; VM, vector magnitude.

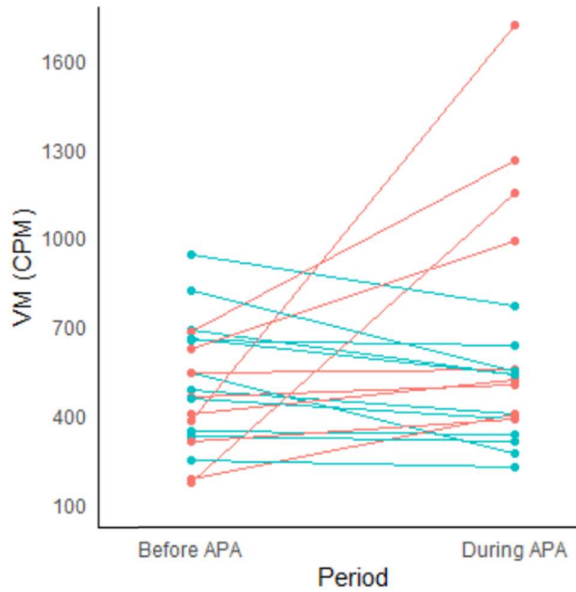


Figure 3 Individual evolution of mean VM during the APA intervention (n = 20).

Red slopes are positive; blue slopes are negative or null.

Abbreviations: APA, adapted physical activity; CPM, counts per minute; VM, vector magnitude.

Table 4 Clinical and PA data before the intervention in the responsive and non-responsive groups.

	Responsive (n=9)	Non-responsive (n=11)	p
General characteristics			
Age (years)	13.0 [8.8 – 17.7]	13.6 [8.3 – 16.9]	0.9
Sex			0.3
Female	2 (22.2)	5 (45.5)	
Anthropometric measures			
BMI z-score	2.42 [0.7 - 10.1]	4.2 [-0.3 - 7.4]	0.9
Obesity	3 (33.3)	6 (54.5)	0.4
PA			
LTPA (h /week)	0 [0 – 6.5]	0 [0 – 6]	0.8
0	5 (55.6)	6 (54.4)	1
VM (CPM)	389.6 [165.2 – 653.8]	520.4 [234.8 – 905.3]	0.2
MVPA (min/day)	52.0 [12.4 - 100.9]	71.6 [31.0 – 138.1]	0.07
≥ 60	3 (33.3)	8 (72.7)	0.2
Questionnaires			

FSSA score	14.0 [8 – 21], n = 9	13.0 [7 – 17], n = 11	0.5
ISI score	6.0 [6 – 14], n = 7	11.0 [1 – 18], n = 10	0.2
NSS-P score	21.5 [16 – 35], n = 8	19.0 [11 – 33], n = 10	0.5
CDI score	17.5 [2 – 22], n = 8	9.5 [2 – 15], n = 10	0.04
Pathological CDI (> 16)	5 (62.5)	0 (0)	< 0.01
VSP-A/E score	56.4 [31.6 – 92.6], n = 8	57.5 [42.7 – 84.3], n = 10	0.7
VSP-P score	68.6 [45.7 – 93.4], n = 8	68.8 [48.9 – 88.0], n = 11	1
Conners F1 (conduct)	51.5 [38 – 84], n = 8	56.0 [39 – 65], n = 11	0.6
Conners F2 (learning)	45.5 [36 – 68], n = 8	43.0 [40 – 67], n = 11	0.7
Conners F3 (psychosomatic)	61.0 [42 – 82], n = 8	56.0 [42 – 104], n = 11	0.7
Conners F4 (impulsivity)	46.5 [39 – 73], n = 8	44.0 [35 – 71], n = 11	0.8
Conners F5 (anxiety)	46.5 [40 – 62], n = 8	45.0 [40 – 73], n = 11	0.4
Conners F6 (hyperactivity)	49.0 [37 – 86], n = 8	49.0 [69 – 67], n = 11	0.8

BLAST

Error rate (%)	4.0 [1 – 10], n = 8	5.0 [0 – 8], n = 10	0.9
Median RT (ms)	727.0 [500 – 976], n = 8	756.5 [491 – 1030], n = 10	0.7
BLAST-Stability	34.5 [23 – 44], n = 8	39.5 [13 – 69], n = 10	0.7
BLAST-Intensity	66.0 [45 – 70], n = 8	61.5 [47 – 81], n = 10	0.9

Data are expressed as median [range] or n (%). FSSA assesses sleepiness, ISI insomnia, NSS-P

narcolepsy severity, CDI depression, and VSP quality of life (VSP-A/E for patients; VSP-P for parents).

Abbreviations: BMI, body mass index; CPM, counts per minute; LTPA, leisure-time physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; RT, reaction time; VM, vector magnitude.

SUPPLEMENTARY MATERIALS

Table S1 Organization of a typical training session provided by the APA teacher.

Exercise 1	Squats x20 repetitions Low speed	Start in a standing position, with your feet placed a little wider than waist width apart, slightly pointing outwards. Lower down in a seating position while keeping your back straight. Repeat.
Exercise 2	Jumping jacks x20 repetitions High speed	In a standing position, spread your legs wider and raise your hands laterally over your head while jumping vertically. Then jump back in starting position. Repeat.
Exercise 3	Elbow plank 30 seconds	On the floor, maintain a plank position on your toes and elbows. Your head, shoulders and hips should be aligned, and your abdominal muscles contracted.

Exercise 4	Burpees x10 repetitions Medium speed	Start in a standing position. Lower down in a push-up position, touching the floor with your chest. Press up to go back in the push-up position. Then jump back on your feet in a standing position with your arms over your head. Repeat.
Exercise 5	Banana plank 30 seconds	Place yourself on the back. Hold your arms straight, off the floor behind your head, while holding your legs straight, off the floor too. Your lower back and your hips should stay on the floor. Maintain the position.

Table S2 Treatments prescribed in the cohort of children with NT1 (n=27).

Molecules	n (%)
Modafinil	1 (3.7)
Pitolisant	4 (14.8)
Methylphenidate	8 (29.6)
Modafinil + Oxybate de sodium	1 (3.7)
Pitolisant + Methylphenidate	7 (25.9)
Oxybate de sodium + Methylphenidate	2 (7.4)
Pitolisant + Oxybate de sodium + Methylphenidate	4 (14.8)

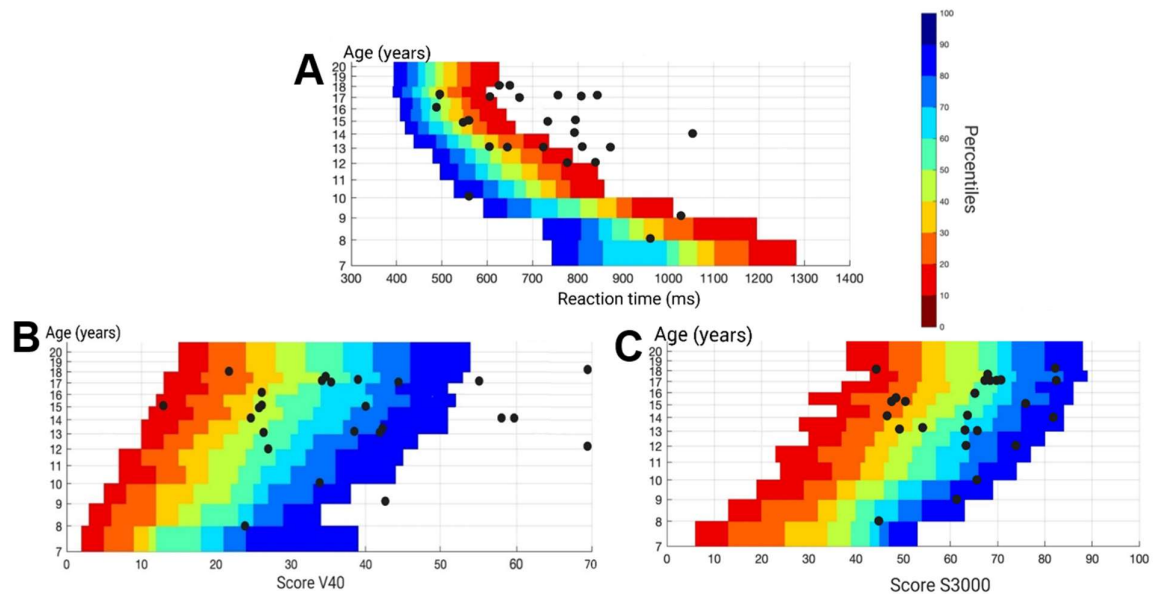


Figure S1 BLAST results at V1 (n = 25). (A) Reaction time; (B) V40 = BLAST-Stability; (C) S3000 = BLAST-Intensity. Colors indicate normative data. Patients are represented as black dots.

Abbreviation: BLAST, Bron-Lyon Attention Stability Test.

Table S3 PA and screen time data according to the type of day (school days and days off) before the intervention.

	School days	Days off	n	P
VM (CPM)	530.9 [192.9 – 976.0]	369.8 [145.3- 831.0]	18	< 0.0001*
Screen time (h /day)	1.5 [0 – 5.5]	4.0 [1 – 10]	15	< 0.01

Data are expressed as median [range].

Abbreviations: CPM, counts per minute; PA, physical activity; VM, vector magnitude.

Table S4 Actigraphic data before and during the intervention (n = 20).

	Before APA	During APA	p
VM (CPM)	454.3 [165.2 – 905.3]	509.5 [215.5 – 1656.3]	< 0.00001*

Data are expressed as median [range].

Abbreviations: APA, adapted physical activity; CPM, counts per minute; VM, vector magnitude.

Table S5 Questionnaire scores and BLAST performance at V1 and V2 for the responsive group.

	V1	V2	n	p
Anthropometric measures	4.1 [0.7 – 10.1]	4.1 [0.8 – 10.5]	8	0.9
BMI z-score	3 (37.5)	3 (37.5)	8	1
Obesity				
Questionnaires				
FSSA score	14.5 [8 – 21]	15.0 [5 – 17]	8	0.4
ISI score	6.5 [6 - 14]	5.5 [2 – 19]	6	0.8
NSS-P score	22.0 [16 – 35]	23.0 [12 – 34]	7	0.8
CDI score	17.0 [2 – 21]	16.0 [2 – 22]	7	0.4
VSP-A/E score	52.4 [31.6 - 92.6]	61.2 [34.2 - 96.7]	7	0.1
VSP-P score	68.5 [45.7 – 93.4]	67.6 [40.3 - 90.3]	7	0.6
Conners F1 (conduct)	56.0 [38 – 84]	53.0 [39 – 87]	7	0.7
Conners F2 (learning)	43.0 [36 – 68]	47.0 [38 – 68]	7	0.6
Conners F3 (psychosomatic)	60.0 [42 – 82]	55.0 [42 – 104]	7	0.7
Conners F4 (impulsivity)	46.0 [39 – 73]	43.0 [39 – 60]	7	0.4
Conners F5 (anxiety)	40.0 [40 – 62]	44.0 [40 – 59]	7	1
Conners F6 (hyperactivity)	51.0 [37 – 86]	45.0 [38 – 86]	7	1

BLAST

Error rate (%)	4.0 [1 – 10]	2.0 [0 – 12]	7	0.7
Median RT (ms)	764 [500 – 976]	661 [547 – 1063]	7	0.4
BLAST-Stability	34.0 [23 – 42]	23.0 [17 – 61]	7	0.9
BLAST-Intensity	66.0 [45 – 70]	58.0 [38 – 85]	7	1

Data are expressed as median [range] or n (%). FSSA assesses sleepiness, ISI insomnia, NSS-P narcolepsy severity, CDI depression, and VSP quality of life (VSP-A/E for patients; VSP-P for parents).

Abbreviations: BLAST, Bron-Lyon Attention Stability Test; RT, reaction time.