Sleep Medicine 15 (2014) 720–723

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Brief Communication

Pilot study on the validity of the pupillographic sleepiness test in children and adolescents

Michael S. Urschitz [a,b,*,1], Katrin Heine [b,1], Lea Mendler [b], Tobias Peters [c], Barbara Wilhelm [c], Christian F. Poets [b]

[a] Unit of Pediatric Epidemiology, Institute of Medical Biostatistics, Epidemiology, and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Germany
[b] Working Group on Pediatric Sleep Medicine, University Children's Hospital Tuebingen, Germany
[c] Pupil Research Group, Centre for Ophthalmology, University Hospital Tuebingen, Germany

ARTICLE INFO

Article history:
Received 4 November 2013
Received in revised form 12 February 2014
Accepted 16 February 2014
Available online 13 April 2014

Keywords:
Central nervous activation
Alertness
Hypersomnia
Sleepiness
Pupillography
Multiple sleep latency test

ABSTRACT

Objective: To report preliminary validation data for the pupillographic sleepiness test (PST) in children and adolescents.
Methods: Twelve patients (13.1 ± 4.4 years of age) underwent the multiple sleep latency test (MLST) and three PSTs at 09:00, 11:00, and 13:00 on one single day. Correlations were tested between mean sleep latency and gender-adjusted *z*-values of the natural logarithm of the pupillary unrest index (zlnPUI).
Results: Spearman's correlation (*P*-value) between the zlnPUI values obtained at 09:00 and 11:00 with the MSL was $r_S = -0.641$ (0.025) and $r = -0.553$ (0.062).
Conclusion: There was satisfactory agreement between PST and the MLST, which is similar to what is found in adults. The PST may be promising for the evaluation of daytime sleepiness in children and adolescents, and should be further evaluated in future studies.

1. Introduction

Excessive daytime sleepiness (EDS) is a widespread problem in children and adolescents and can have major negative effects on performance, health, and safety [1]. Evaluations usually include some kind of structured sleep history, sleep logs, sleep questionnaires, and objective tests for the state domain of EDS (eg the multiple sleep latency test [MSLT] [2].

Lowenstein et al. were the first to observe typical fluctuations in pupil size in sleepy adults [3], and the first clinical application of pupillography was in narcolepsy [4]. The pupillographic sleepiness test (PST) is a standardized, accurate, and reliable physiological test for the level of EDS in adults [5] and has also been discussed for the laboratory assessment of EDS in children [6,7]. However, feasibility and accuracy of the PST are unknown in pediatric patients, hampering its widespread pediatric use.

As part of an interdisciplinary project (TUPEDS: Tuebingen Project on EDS in Childhood), we had demonstrated the feasibility of the PST in a field setting and reported preliminary reference values for the pupillary unrest index (PUI), the main sleepiness parameter of the PST [8]. In the current report from TUPEDS, we present preliminary validation data for the PST.

2. Methods

2.1. Study design

A prospective diagnostic test pilot study was performed with the MSLT as reference standard and the PST as index test. Patients underwent a standard overnight polysomnography in a sleep laboratory, followed by multiple PST and MSLT assessments the next day. The study design was approved by the Ethics Committee of Tuebingen University Hospital; written informed parental and child's consent were obtained. The pilot study was stopped after 12 patients, and an interim analysis was performed.

2.2. Subjects

Eligible subjects were children referred to the sleep disorders center of the University Children's Hospital Tuebingen between October 2011 and January 2013. Inclusion criteria were: (i) 6–18 years of age and (ii) history of EDS and/or referral for the

* Corresponding author. Address: Unit of Pediatric Epidemiology, Institute of Medical Biostatistics, Epidemiology, and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Obere Zahlbacher Str. 69, 55131 Mainz, Germany. Tel.: +49 6131 17 3122; fax: +49 6131 17 2968.
E-mail address: urschitz@uni-mainz.de (M.S. Urschitz).
[1] M.S. Urschitz and K. Heine contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.sleep.2014.02.008
1389-9457/

evaluation of EDS. Exclusion criteria were: (i) developmental or cognitive disorder impairing patient's compliance and (ii) restricted pupillary motility.

2.3. PST

A detailed description of the PST is given elsewhere [5,8]. In short, the PST was performed according to standard operating procedures established in adults [9]. The procedures were not modified for application in children. Measures were obtained three times at 2 h intervals starting at 09:00. Recordings of spontaneous pupillary oscillations were acquired for 11 min by infra-red video pupillography in a fully darkened and quiet room [5]. During the test, subjects fixated a red light source at the lens aperture of the video camera in an upright position. To block ambient light fully, subjects wore goggles with black lenses and infrared filters. Pupillary oscillations were registered, quantified, and analyzed automatically by the system [10]. The entire 11 min recording was divided into eight segments each comprising 82 s recording time and 2048 data points. Before off-line analysis, missing data values were replaced by linear interpolation. The amount of interpolation was calculated as percentage of recording time. A sufficient recording quality was defined as interpolation <40% of recording time [8]. Based on the pupil diameter, the PUI (mm/min) was calculated, which corresponded to a low pass filtering of the data set [10]. In the present study, PUI trend data were printed out and visually inspected for artifacts by two of the authors (B.W., T.P.). Artifacts were handled and PUI manually recalculated according to a previously described protocol without knowledge of MSLT results [8]. Higher PUI values corresponded to more sleepiness. Immediately after each PST, subjective sleepiness was investigated using a German version of the Stanford Sleepiness Scale (SSS) [11]. A higher SSS value corresponded to more sleepiness.

2.4. MSLT

The MSLT was performed according to a current guideline [12]. It included three to five 20 min nap attempts at 2 h intervals starting at 09:30, shortly after performance of the PST. Manual scoring was performed by one of the authors (M.S.U.), who was blinded to PST results. The sleep latency to the first epoch of sleep was calculated on each nap attempt and the mean sleep latency (MSL) computed across all naps, assigning 20 min for those periods in which no sleep was obtained. A shorter MSL corresponded to more sleepiness.

2.5. Statistical analysis

Descriptive statistics including mean, standard deviation (SD), and range were used to summarize demographic and clinical characteristics. To obtain a normal distribution, the natural logarithm of the PUI (lnPUI) was calculated. To account for gender differences in children, lnPUI values were transformed into lnPUI *z*-values (*z*-lnPUI) using the mean and SD of previously obtained pediatric reference values (i.e. 2.01 ± 0.43 for boys and 1.93 ± 0.43 for girls) and the formula: *z*-lnPUI = (lnPUI − mean)/SD [8]. In accordance with the MSL, intra-individual means were calculated for lnPUI, *z*-lnPUI, and SSS. Time-of-day variations were assessed by scatter plots and fitting lines of simple linear regression. Agreement of the mean *z*-lnPUI and the three single *z*-lnPUI values obtained at 09:00, 11:00, and 13:00 with the MSL and the three single SSS values was evaluated using Spearman's rank correlation coefficient, r_S. Due to the exploratory character of the pilot study, no sample size calculation and no statistical hypothesis test was performed. Hence, *P*-values for r_S were calculated for illustrative purposes rather than hypothesis testing. All analyses were done with statistical software (IBM SPSS Statistics 20).

3. Results

Twelve children (five boys, seven girls) with a mean ± SD age (range) of 13.1 ± 4.4 (7–18) years were enrolled and 36 PST recordings successfully performed (Table 1). No recording was terminated prematurely. Interpolation ranged from 1.2% to 67.1% of recording time (mean ± SD, 14.1 ± 15.3). Only one recording had an interpolation of >40%; this child was extremely sleepy,

Table 1
Clinical characteristics of study patients (n = 12).

No.	Sex	Age (years)	Diagnosis	Mean sleep latency (min)	SOREMPs (no.)	Mean SSS	lnPUI (*z*-lnPUI)			Mean lnPUI	Mean *z*-lnPUI
							09:00	11:00	13:00		
1	Female	11	Narcolepsy with cataplexy	1.1	>2	4.7	2.74 (+1.88)	2.63 (+1.63)	2.53 (+1.40)	2.63	+1.64
2	Female	11	Unclear excessive daytime sleepiness	5.1	1	4.0	3.00 (+2.49)	2.95 (+2.37)	2.97 (+2.41)	2.97	+2.42
3	Female	17	Suspected idiopathic hypersomnia	2.5	0	3.3	3.49 (+3.63)	2.38 (+1.05)	2.44 (+1.19)	2.77	+1.96
4	Female	7	Obstructive sleep apnea	20.0	0	2.3	2.17 (+0.57)	2.12 (+0.45)	2.25 (+0.75)	2.18	+0.59
5	Male	18	Insufficient sleep syndrome	6.5	1	3.3	1.42 (−1.37)	1.20 (−1.88)	0.72 (−2.99)	1.11	−2.08
6	Female	14	Obstructive sleep apnea	1.6	0	4.0	3.23 (+3.02)	2.52 (+1.37)	2.41 (+1.12)	2.72	+1.84
7	Male	12	Suspected narcolepsy without cataplexy	8.4	0	2.7	2.50 (+1.14)	2.32 (+0.72)	1.74 (−0.62)	2.19	+0.41
8	Female	18	Chronic fatigue	16.8	0	3.0	1.76 (−0.40)	1.89 (−0.10)	1.96 (+0.06)	1.87	−0.15
9	Male	14	Insufficient sleep syndrome	2.8	2	3.3	2.71 (+1.64)	2.85 (+1.95)	2.06 (+0.12)	2.54	+1.23
10	Male	10	Periodic limb movement disorder	17.0	0	2.7	2.47 (+1.08)	2.40 (+0.91)	2.76 (+1.75)	2.55	+1.25
11	Female	13	Narcolepsy with cataplexy	8.0	3	3.0	1.59 (−0.80)	1.36 (−1.33)	1.65 (−0.65)	1.53	−0.92
12	Male	10	Habitual snoring	20.0	0	2.0	2.25 (+0.55)	2.36 (+0.81)	2.44 (+1.00)	2.35	+0.79

SOREMPs, sleep-onset rapid eye movement periods; SSS, Stanford Sleepiness Scale; PUI, pupillary unrest index; ln, natural logarithm.