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Research article

Neurological soft signs in primary headache patients

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HIGHLIGHTS

- Neurological soft signs (NSS) are clinical markers of minor brain alterations.
- NSS are increased in primary headache outpatients (HP).
- NSS are increased in HP expressing white matter hyperintensities at brain imaging.
- Headache type and characteristics do not influence NSS presentation.
- NSS identify a subset of primary HP sharing brain anomalies and comorbidities.

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ABSTRACT

Neurological soft signs (NSS) are semeiotic anomalies not assessed by the standard neurological examination, primarily developed in psychiatric settings and recently proposed as potential markers of minor brain circuit alterations, especially the cerebellar–thalamic–prefrontal network. Primary headache patients present with normal neurological examination and frequent psychiatric comorbidity. Aim of this exploratory study consisted in assessing NSS in 20 episodic frequent migraine (MH) and in 10 tension-type headache (ETTH) outpatients compared to 30 matched healthy controls. NSS were assessed by the Heidelberg scale; clinical characteristics and brain MRI were additionally obtained in all patients. NSS were increased by ~70 and ~90% in ETTH and MH, respectively, with respect to controls ($p < 0.001$) and the difference remained significant even after controlling for age and education. Headache type and characteristics did not influence NSS presentation, while headache patients with white matter hyperintensities (WMH) at brain MRI had higher NSS scores compared both to normal controls and patients without WMH. NSS identify a subset of primary headache patients sharing the same comorbidities or minimal brain anomalies, suggesting that tailored prophylactic options might apply.

1. Introduction

Neurological soft signs (NSS) are minor semeiotic anomalies not assessed during the standard neurological examination and for a long time postulated to indicate a diffuse dysfunction within the nervous system [1]. A more recent concept assumes the presence of micro-anomalies within more specific brain networks [2,3]. In particular, studies suggest the NSS might predict abnormalities within the cerebellar–thalamo–prefrontal circuitry [4,5] and be viewed as an index of "cognitive dysmetria" [5,6]. NSS assessment encompasses different domains, such as motor coordination (*e.g.*, finger-to-nose test or diadochokinesis), up to complex motor sequences (*e.g.*, Ozeretzki's or Luria's tests), and often include also sensory integration (*e.g.*, stereognosis or graphesthesia). Furthermore some NSS scales include the assessment of primitive reflexes as well (*e.g.*, snout or Myerson reflexes).

NSS have been studied extensively in the field of psychiatry, and mainly of schizophrenia [7]; accordingly, several authors considered them as a potential marker for endophenotypes of psychotic conditions, being already present before transition to psychosis in at-risk individuals to the same extent as after transition [8] and even among non psychotic relatives in affected pedigrees [9].

By contrast, NSS expression has been rarely addressed in the field of neurology, possibly because the concept of a neurological semeiotics failing to localize lesions is in dramatic contrast with its founding principles [10]; the only notable exceptions relate to NSS correlations with specific cognitive functions and impairments, mainly of the executive type [11–13].

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Table 1
Demographic and clinical data. CTRL, healthy controls; ETTH, frequent episodic tension-type headache; MH migraine; NP, not performed; PROF, prophylaxed primary headache patients (including 3 MH and 2 ETTH). Data are reported as mean ± SD (range).

	CTRL $n=30$	MH $n=20$	ETTH $n=10$	PROF $n=5$
Sex, M/F	7/23	4/16	3/7	2/3
Age, years	39.7 ± 12.1 (22–72)	40.3 ± 9.3 (25–57)	39.1 ± 16.6 (23–74)	40.6 ± 13.7 (26–62)
Education, years	13.1 ± 3.2 (5–18)	12.7 ± 2.5 (8–18)	12.2 ± 5.8 (5–23)	11.2 ± 3.5 (5–13)
HDI	NP	47.1 ± 12.1 (26–72)	40.6 ± 12.6 (28–64)	NP
Symptomatic drugs, *n*/month	NP	9.4 ± 5.9 (4–30)	8.6 ± 3.5 (4–14)	NP
Frequency, *n* attacks/month	NP	8.9 ± 3.5 (4–14)	8.8 ± 3.3 (4–14)	NP

Primary headaches are very prevalent conditions that imply high social and personal costs with the constant need of developing effective therapeutic strategies [14]. Standard neurological examination in these disorders is almost always not informative and often brain imaging studies are requested in order to reach an exclusion diagnosis. Often these conditions are co-morbid to mood disorders [15], besides other psychiatric diseases, due to a mix of psychological adaptation to frequent pain, genetic predisposition, and neurotransmitter imbalance [16–18].

The availability of endophenotypes for psychiatric conditions in primary headache patients might be useful for further exploring boundaries between these conditions and testing drugs more rationally. Therefore, the primary aim of this pilot work consisted in assessing NSS in primary headache patients with respect to healthy matched controls, assessing as secondary aims the relationship between NSS scores and headache characteristics both clinical and of brain imaging.

2. Methods

In this exploratory case-control study, 30 consecutive primary headache patients (HP) were recruited following informed consent during the headache-free period from the outpatients afferent to the Neurology Unit. Inclusion criteria were: (a) diagnosis of migraine (MH) with or without aura or frequent episodic tension-type headache (ETTH) according to current criteria from the International Headache Society [19]; (b) age >18 and <75 years old; (c) history of at least 10 episodes and number of attacks ≥1 and <15/month; (d) no current prophylaxis or other psychoactive medications; (e) no previous history of neurological or psychiatric disorders other than headache; (f) a fully normal standard neurological examination.

For both MH patients ($n=20$) and ETTH ones ($n=10$) number of attacks/month and number of over-the-counter medication/month referring to the previous three months period were recorded; patients were also asked to complete the headache disability inventory (HDI) [20]. Only one MH patient reported more than 15 symptomatic drugs/month (specifically $n=30$), raising the suspect of a concomitant medication-overuse headache. Considering the exploratory nature of this study and the impossibility of a formal *a priori* power calculation, the recruited sample size was considered sufficient for generating the reported preliminary data.

Furthermore, 5 primary headache patients (3 MH and 2 ETTH) taking amitriptyline 10 mg o.d. as prophylaxis (PROF) were recruited *post hoc* in order to explore the potential contributory role on the NSS score of the exposure to anticholinergic and sedative medications.

Finally, healthy controls (CTRL) were age- (±2 years) and sex-matched and education-comparable and they were recruited from the spouses of other neurological outpatients. They had no previous history of neurological or psychiatric disorder (including significant headache), nor were they under psychoactive medications. Demographic and clinical data are included in Table 1.

Besides a complete neurological examination, all patients were also evaluated for NSS. The examination was carried out in a calm environment, without interruptions or additional observers. Among the available tools [21], we choose the 16-items Heidelberg scale [22] since, unlike other batteries, it excludes primitive reflexes. These are, in fact, automatic responses marking, more properly, cognitive and upper motor neuron dysfunctions [23]. As so, they are qualitatively different from the core NSS, mainly addressing sensorimotor integration and coordination [22]. In the Heidelberg scale, the examination procedure is so chosen that the initial tests are carried out with the patient in a standing position. The patients' ability to perform a given exercise is scored on a 4-point scale, from 0 (no difficulties) up to 3 (marked difficulties). The Heidelberg scale explores five different subdomains, as follows: (1) motor coordination, including: Ozeretski's test, diadochokinesis, pronation–supination, finger-to-thumb opposition, speech and articulation, (2) integrative functions, including: gait, tandem walking, two-point-discrimination, (3) complex motor tasks, including: finger-to-nose test, fist-edge-palm-test, (4) right/left and spatial orientation, including: right/left orientation, graphesthesia, face-hand test, stereognosis, (5) hard signs, including: arm holding test, mirror movements. In the original report, this scale was found to have a high internal reliability (Cronbach's alpha 0.83) and a high inter-rater reliability (0.88) [22].

All patients also underwent a brain MR scan (1.5 T), including axial FLAIR sequence (slice thickness 5 mm with a gap of 1 mm; TR 6000 ms/TE 120 ms; field of view: AP 230 mm/RL 183 mm/FH 155 mm), performed in order to provide whole brain coverage. Images were assessed blindly and the Fazekas scale applied to qualitatively score white matter hyperintensities (WMHs), dividing them in periventricular white matter, and deep white matter (DWM) signal alterations [24].

Statistical analysis was performed by SPSS. NSS differences among the recruited groups were assessed by ANCOVA followed by Bonferroni *post hoc* test, controlling for age and education. Two-tailed Student's *t*-test, ANOVA followed by Bonferroni and Pearson analysis of correlation were used as appropriate.

3. Results

The impact of age on the NSS score was initially determined in the group of CTRL ($n=30$). However, since the age of the recruited subjects distributed unevenly in the older group, we recruited 8 more elderly controls. The whole group of CTRL subjects ($n=38$) displayed a very strong correlation with the NSS scores ($r=0.91$ $p<0.0001$). A similar albeit less strong correlation was present in primary HP ($r=0.31$ $p=0.01$ $n=20$ and $r=0.65$ $p<0.005$ $n=10$, for