Pain Ther (2023) 12:1135–1148
https://doi.org/10.1007/s40122-023-00532-y

ORIGINAL RESEARCH

The Occipital Nerves Applied Strain Test to Support Occipital Neuralgia Diagnosis

Boaz G. Samolsky Dekel · Maria C. Sorella · Alessio Vasarri · Rita M. Melotti

Received: March 29, 2023 / Accepted: May 25, 2023 / Published online: June 13, 2023

ABSTRACT

Introduction: Occipital neuralgia (ON) is a disabling cephalalgia form with demanding diagnostic workflow. We report the description and reliability analyses of the occipital nerves-applied strain (ONAS) test for occipital neuralgia (ON) early-stage diagnosis in cephalalgia patients.

Methods: In a retrospective and observational study, we evaluated, among $n = 163$ consecutive cephalalgia patients, the sensitivity, specificity, and prior probability [positive (PPV) and negative (NPV) predictive values] of the ONAS test against two reference tests (occipital nerve anesthetic block and the painDETECT questionnaire). Multinomial logistic regression (MLR) and χ^2 analyses verified the ONAS test outcome's dependence upon independent variables (gender, age, pain site, block test, and painDETECT outcomes). We assessed inter-rater agreement with Cohen's kappa statistic.

Results: ONAS test showed sensitivity and specificity of 81 and 18%, respectively, against the painDETECT and of 94 and 46%, respectively, against the block test. PPV was > 70% against both tests, while NPV was 81% against the block test and 26% against the painDETECT. Interrater agreement Cohen's kappa was excellent. Significant association (χ^2 analyses) and relationship (MLR) were found only between ONAS test and pain site but not with the other independent predictors.

Conclusions: The ONAS test showed satisfactory reliability among cephalalgia patients; thus, it might be considered a valuable early stage tool for ON diagnosis in these patients.

Boaz G. Samolsky Dekel, Maria C. Sorella, Alessio Vasarri and Rita M. Melotti contributed equally to this work.

B. G. Samolsky Dekel (✉) · M. C. Sorella · R. M. Melotti
Department of Medicine and Surgery Sciences, University of Bologna, Via Massarenti N. 9, 40138 Bologna, Italy
e-mail: boaz.samolskydekel@unibo.it

B. G. Samolsky Dekel · M. C. Sorella · A. Vasarri · R. M. Melotti
Anesthesia and Pain Therapy Unit, IRCCS Azienda Ospedaliera-Universitaria Di Bologna Policlinico S. Orsola-Malpighi, Via Massarenti N. 9, 40138 Bologna, Italy

B. G. Samolsky Dekel · R. M. Melotti
Post Graduate School of Anaesthesia and Intensive Care, University of Bologna, Via Massarenti N. 9, 40138 Bologna, Italy

PLAIN LANGUAGE SUMMARY

We report the description and reliability features of an occipital neuralgia diagnostic tool. The latter is based on the assertion that applying a strain on putatively compromised

occipital nerves prompts abnormal nerve discharges and subjective pain reactions and thus may reveal occipital neuralgia. Among 163 cephalalgia patients, the test showed sensitivity and specificity of 81 and 18%, respectively, against the painDETECT questionnaire and 94 and 46%, respectively, against the occipital nerves' block test. Interrater agreement was excellent, and significant associations and relationships were found only between the tool and congruent pain site but not with the other independent predictors. This tool may help clinicians' early detection of occipital neuralgia in cephalalgia patients.

Keywords: Occipital neuralgia; ONAS test; PainDETECT; Anesthetic block; Reliability

Key Summary Points

Why carry out this study?

Occipital neuralgia (ON) is a disabling cephalalgia form with demanding early diagnostic workflow.

We report the description of the occipital nerves applied strain (ONAS) test and analyzed its reliability as an adjunctive tool for ON early stage diagnosis in cephalalgia patients.

What was learned from the study?

The ONAS test showed satisfactory reliability (sensitivity, specificity, prior probability, and interrater agreement) among cephalalgia patients.

What has been learned from the study?

With its ease of execution and demonstrated reliability, the ONAS test might be considered a valuable early stage tool for ON diagnosis in cephalalgia patients.

INTRODUCTION

Occipital neuralgia (ON) is a disabling form of cephalalgia, classified among "painful cranial nerves and other facial pain lesions" and commonly arise from putatively compromised occipital nerves [1]. ON negatively affects patients' quality of life, workability, and social relations. As such, it has critical healthcare and social costs [2]. ON incidence is as high as 3.2 cases per every 100,000 individuals, and it increases after 50 years of age; roughly 80% of ON patients are females [1].

The nerves primarily involved in occipital neuralgia are the greater occipital nerve (GON), the lesser occipital nerve (LON), and the third (or least) occipital nerve (TON).This group of nerves arises from the C2 and C3 spinal nerves. It innervates the posterior scalp up to the vertex, the ear, and the skin above the parotid gland. The LON innervates the scalp lateral region behind the ear and the ear's cranial surface. The TON also innervates the C2–C3 facet joint spinal nerves and part of the semispinalis capitis [3, 4].

In their peripheral distribution, occipital nerves have particular relationships with local bones, arteries, and muscles. These relationships make the occipital nerves potential sources of nerve compression, entrapment, irritation, or subject to whiplash injuries and posture imbalances [5]. Consequently, occipital nerves are commonly associated with ON, cervicogenic, and migraine cephalalgia [4]. ON, in particular, may present with shooting or stabbing pain in the occipital nerve's dermatomes and tenderness over the involved nerve [1]. The pain spreads from the suboccipital region to the vertex, particularly involving the upper neck, the head's posterior aspect, and the fronto-orbital area. Hypesthesia or dysesthesia may accompany the pain in the affected areas [4]. The GON is involved in roughly 90% of ON cases; in approximately 10% of cases, LON or both GON and LON are involved [6, 7].

Cervical pain pathophysiology may include nociceptive and neuropathic pain (NeP) conditions [8]. The former comprises pure nociceptive pain and somatic-referred pain, while the

latter radicular pain and radiculopathy [9]. In particular, nociceptive cervical pain is due to nociceptor activation within cervical spine structures. Somatic referred pain arises when activated afferents converge onto the spinal cord second-order neurons that subtend cervical areas. Afferents of an injured dorsal root, ganglion [8], or peripheral nerve displaying ectopic and heterospecific discharges, cause radicular pain [10–12]. Conducting a block of a spinal nerve or its roots can alleviate radiculopathy.

Neurological signs and symptoms characterize radicular pain and radiculopathy [8]. As in the literature, "radicular pain shows dysesthesias with qualities of lancinating or electric shock sensations. Radiculopathy is accompanied by paresthesia (tingling, skin crawling, or pins and needles feeling) and negative signs like compromised reflexes, numbness, and weakness when sensory or motor fibers are injured. Allodynia may also be present [13]." In this paper, neuralgia refers to any pain in the distribution area of dysfunctional or injured nerves, encompassing both paroxysmal and non-paroxysmal pain[1].

Given the possible coexistence of variable ON pathophysiology and clinical patterns, the differential diagnosis may be challenging—in particular, the distinction between ON and somatic-referred pain. The latter may arise from the "atlantoaxial and upper zygapophyseal joints or tender trigger points in neck muscles [1]". Thus, an ON diagnosis should be guided by a thorough history taking, clinical examination, and an accurate neurological study with appropriate clinical tests [1]. Occipital nerve anesthetic block is often used for ON diagnosis and treatment. Nonetheless, it requires patient consent and adequate professional and clinical context, which are not always promptly available at the early stage of ON diagnostic workflow.

We report the description and reliability analyses of an adjunctive clinical test, the occipital nerves applied strain (ONAS) test, which may contribute to ON differential diagnosis in cephalalgia patients. We hypothesized that the ONAS test would show satisfactory reliability as an ON diagnostic tool within a cohort of cephalalgia patients.

METHODS

Settings and Patients

This observational and retrospective reliability study was held at the Chronic Pain Center of Bologna's University Teaching Hospital (IRCCS, S. Orsola-Malpighi polyclinic, Bologna, Italy). Inclusion criteria were chronic cephalgia ($\geq$ 3 months) outpatients with at least one diagnostic occipital nerve anesthetic-block test in the follow-up visits, $\geq$ 18 years of age, and signed informed consent. Exclusion criteria were history or diagnosis of cancer or diabetes upon first visit or follow-up visits, Short Portable Mental Status Questionnaire (SPMSQ) score $<$ 8, and patients with clinical or imaging signs for cervical hernia conditions. The sample hence includes n = 163 consecutive non-cancer cephalalgia patients.

Proceedings and Instruments

As described in our previous reports, "routinely, upon the first visit and before the physical examination, patients fill out three questionnaires: the SPMSQ, (to screen cognitive dysfunctions and abilities), the Brief Pain Inventory (BPI, to evaluate patients' pain intensity and its interference with quality of life), and the painDETECT (PD) questionnaire; patients are thoroughly instructed on the meaning and how to interpret and fill out the questionnaires. Thereafter, a focused clinical history and physical examination for cephalalgia patients are taken. In the latter, the ONAS test is included. Finally, results of the clinical examination and tests are discussed with the patient and congruent therapeutic measures are hence taken [13, 22]". Upon follow-up, and before the physical examination or any therapeutical procedures, patients fill out the PD and BPI questionnaires once more. The retrieved clinical information from each visit, including questionnaires and test outcomes, is stored in the

patient's chart and the clinic's database. According to the inclusion/exclusion criteria (see below), the sample was pooled out of the clinic's database, which includes clinical records of chronic pain patients and covers records from May 2014 to December 2022.

Cephalgia patients who did or did not test positive with the ONAS test are hence scheduled for diagnostic occipital nerve anesthetic block. In this study, we report only the ONAS test, PD questionnaire, and the block test outcomes.

Pathophysiological Rationalization of the ONAS Test

Nerve injury alters the nerve's structure and functioning due to the nerves' healing biological responses. The latter amplifies abnormal responses to noxious and innocuous stimuli resulting in a NeP condition with spontaneous dysesthesias and paresthesia [14].

In animal studies, applying a strain (squeezing or pressure) onto normal nerve roots evokes only limited discharges. However, pressures over an inflamed/injured dorsal ganglion, dorsal root, or nerves prompt abnormal discharges in an ample afferents spectrum [15–17]. Notably, persistent nerve ligature promotes axonal atrophy, and "atrophic nerve fibers distal to a persistent constriction are particularly susceptible to local pressure [18]."

In humans, percussing putatively compromised distal nerves may elicit dysesthesias (Tinel's sign) [19, 20]. The latter is frequently observed in injured nerve conditions and relates to the nerve regeneration process [11, 12].

Finally, the "Valleix's points" refer to "different points along the course of a nerve, about which applied pressure causes pain in cases of neuralgia [21]." In particular, pressure applied onto injured occipital nerves' peripheral branches may evoke or exacerbate the patient's pain.

Given the above, we reasoned that a strain applied on a putatively compromised occipital nerve might evoke abnormal discharges and subjective responses, thus giving evidence of the presence of ON. We have proposed a similar approach (the BUAS test) to uncover radicular pain in lower back and limb pain [13, 22]. For ON diagnosis, we propose applying a strain onto the occipital nerves when crossing the nuchal line, i.e., the ONAS test.

The ONAS Test

Landmarks for the ONAS test implementation are shown in Fig. 1 and include the occipital external protuberance (OEP), the mastoid process (MP), and the inferior nuchal line (INL). Standing behind the patient in the sitting position, the examiner traces a line between the OEP and the MP (Fig. 1, dashed lines a to b). The OEP-MP line is divided into medial, intermediate, and lateral thirds (Fig. 1, arrows). The intersection of this line's lateral and medial thirds with the INL (Fig. 1, points c and d, respectively) correspond to the passage of the LON and GON, respectively. Points c and d, just

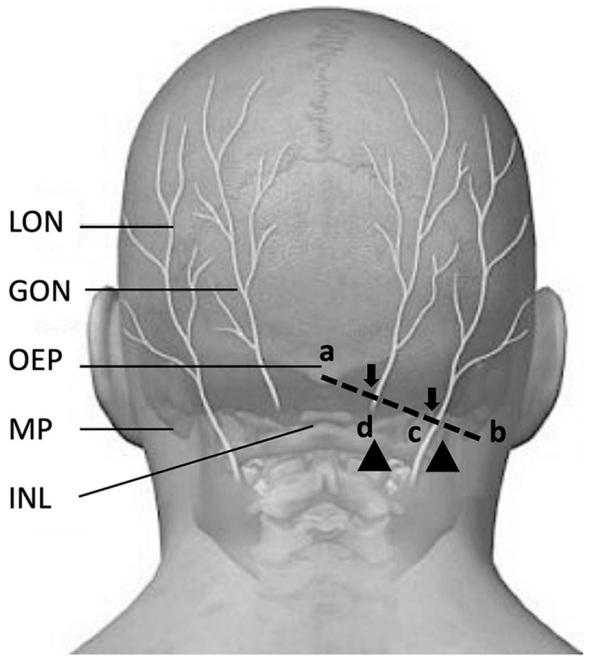

Fig. 1 Semi-schematic anatomical illustration of the ONAS test landmarks. *LON* lesser occipital nerve, *GON* greater occipital nerve, *OEP* occipital external protuberance, *MP* mastoid process, *INL* inferior nuchal line. *Dashed line* a to b: traced between the *OEP* and the MP; *Arrows* lateral ends of the medial and intermediate thirds of line a–b. *Arrowheads* (points c and d), areas, just below the INL, onto which the ONAS test strain should be applied

below the INL, represent the areas onto which the strain should be applied for the ONAS test (Fig. 1, arrowheads). A practical version of the ONAS test, used in this study, is to identify, with the examiner's index, the OEP and with his/her thumb, the MP. With the examiner's index kept on the OEP, the thumb moves medially along the INL to point c (lateral-third's medial end) and afterward to point d (vertical projection of the medial-third's lateral end of the EOP-MP line onto the INL). At both points, the thumb exerts the needed pressure (i.e., the strain) to reach the INL, hitting the occipital LON and GON nerves, respectively. The ONAS test is positive if the patient reports sharp pain onset distinct from the mere pressure.

Diagnostic Block The risks and benefits of the procedure are explained to the patient before written informed consent is obtained. The block is delivered in an adequately equipped context and under a sterile surgical preparation to preserve patient safety. The patient is seated or prone with the neck roughly flexed. The intervention area is prepared using povidone-iodine or chlorhexidine. The landmark is the OEP. The GON is identified as roughly 2 cm caudal and 2 cm lateral to the OEP (about one-third of the OEP to the MP line). We use a 5-ml syringe with a 25-gauge needle. The needle is directed to the GON following a caudal-lateral approach. The needle tip is gently advanced until resistance from the periosteum is encountered. After withdrawing the needle for 1 mm, aspiration is made to ensure no contact with the occipital artery. One milliliter of bupivacaine 0.5% is hence injected. GON block is successful if pain reduction is $\geq$ 50% after 20 to 30 min.

Demographic and Clinical Predictors

As described in our previous reports, "demographic predictors are (I) gender: male/female; (II) age groups [in order to avoid unbalanced over-representation in wider age interval groups, patients over 35 years of age are divided into 15-year interval subsets: 36–50; 51–65; 66–80, and $\geq$ 81 years (classes B–E, respectively); the only subset having a 17-year interval is that of young adults, i.e., 18–35 years of age (class A)] [13, 22]."

We retrieved pain-related predictors from the BPI along with the ONAS test, PD, and block outcomes. The BPI human body scheme allows pain site anatomical localization. Pain conditions and site categories were cephalalgia alone or associated with either fibromyalgia, herpes zoster, lower back pain, nuchal pain, nuchal and upper limb pain, and other pain sites.

As in the literature, "the PD is a clinician-administered and patient-reported screening questionnaire to reveal the likelihood of a NeP component in ON patients. It consists of seven items that address neuropathic-pain symptoms' quality, with a final score between − 1 and 38 (a score of $\leq$ 12 implies no neuropathic component, a score of $\geq$ 19 implies the presence of neuropathic component, while a score of 13–18 implies that the result is uncertain (yet, not negative) [23–25]."

As described in our previous reports, "in this study, we first report both PD negative, uncertain, and positive outcomes. For the reliability analyses and the construction of 2 $\times$ 2 contingency tables, we considered uncertain and positive outcomes as positive ones [13, 22]."

Ethics

The study's data collection was authorized by the Bologna's University Teaching Hospital, (IRCCS, S. Orsola-Malpighi polyclinic, Bologna, Italy) Ethics Committee (# 235/2013/O/Oss) and conducted according to the Helsinki Declaration of 1964 and its later amendments and the International Association for the study of Pain (IASP)'s guidelines for pain research in animals and humans. The investigators personally and thoroughly informed all participants of the study's aims. Patients were informed that participation was voluntary and anonymous and would not affect their care;

hence, informed consent was obtained to retrieve data from the patient's chart.

Data Presentation and Statistical Analysis

We report continuous data as the mean (± SD, standard deviation) and category data as absolute numbers and percentages. The ONAS test outcome's dependence upon independent variable categories (gender, age group, pain site, PD, and block test outcomes) was determined using χ^2 analysis. We performed a post hoc cell contribution analysis for significant associations, and significant contributions for the association were reported. Multinomial logistic regression (MLR) was used to classify subjects based on a set of predictor variables. Dependent variables for MLR were the ONAS test outcome classes, where the 'positive' class (the most numerous) was the reference outcome class. Independent variables were those used for the above-mentioned χ^2 analysis. Statistical significance was defined as $p < 0.05$. When appropriate, three-decimal p values are reported.

The ONAS test reliability was evaluated by its sensitivity, specificity, and the prior probability against the PD questionnaire and block test outcomes [26]. Following the literature, "Prior Probability is defined by calculating the positive predictive value (PPV) and the negative predictive value (NPV). These terms describe the likelihood (positive or negative, respectively) of the condition of interest given the positive or negative test result [27]".

As in the literature, "sensitivity, specificity, PPV, and PNV are expressed in percentages and their upper and lower confidence intervals (CI) and margin of error (M). The latter is one-half of the width of the CI and summarizes the width of a CI relative to the whole possible range [28]".

The ONAS test interrater reliability was evaluated in a subsample of 30 consecutive patients. Raters were two senior pain clinicians and five instructed anesthesia residents. The raters formed ten pairs of a senior clinician and a resident; each resulting pair evaluated three successive patients, being the pair components blinded to each other's evaluations. Interrater agreement analysis was thus based on 60 observations. Among the latter, we have defined the prevalence of the index condition (positive ONAS test) and the overall agreement percentage. We applied Cohen's kappa test for agreement analysis. When significant, an absolute kappa value (with its standard error, SE) of 0.1–0.3 is considered mild agreement; 0.31–0.5 as moderate; and 0.51–1.0 as excellent [26].

RESULTS

The sample included 163 patients with a mean age of 60.9 (± 16.7; range, 19–95) years; 74.7%

Table 1 Demographic and clinical features of the study's sample

	n **(%)**
Sample	163 (100.0)
Gender	
Male	41 (25.3)
Female	122 (74.7)
Age group (years)	
A (18–35)	11 (6.7)
B (36–50)	38 (23.3)
C (51–65)	41 (25.2)
D (66–80)	53 (32.5)
E (> 80)	20 (12.3)
Pain site	
CFM	4 (2.5)
CHZ	3 (1.8)
CL	17 (10.4)
CN	64 (39.3)
CNUL	37 (22.7)
CP	38 (23.3)

CM cephalgia and fibromyalgia, *CHZ* cephalgia and herpes zoster, *CL* cephalgia and lower back pain, *CN* cephalgia and nuchal pain, *CNUL* cephalgia nuchal and upper limb pain, *CP* cephalgia associated with other specific pain sites

(n = 122) were females (Table 1). The most frequent pain condition and localization was cephalgia associated with nuchal pain 39.3% (n = 64) or upper limb pain 22.7% (n = 37).

Table 2 reports the frequency distribution of the ONAS test, block test, and PD outcomes. It also reports the number of even cases (i.e., concordance between the block test, ONAS test, and PD outcomes). Of the sample, 81.0% (n = 132) tested positive on the ONAS and the block tests. Cases that tested negative on the block test, ONAS test, and PD (i.e., even negative cases) were only 4.9% (n = 8). Interestingly, among the cases that tested negative on the ONAS and the block tests, 14.1% (n = 23) tested positive or uncertain on the PD.

Finally, of the patients who tested positive on the block and ONAS tests, 15.2% (n = 20) tested uncertain on the PD. Considering the PD 'uncertain' outcome a positive one, cases that tested positive on the block test, ONAS test, and PD (i.e., even positive cases) were 58.9% (n = 96).

Associations and MLR

The ONAS test outcomes and the independent predictors association analyses (χ^2-analysis) results are reported in Table 3. The latter also reports the post hoc analysis results as cell contributions for significant associations (the two most influential contributions). Significant associations (χ^2-analysis, $p < 0.0001$, respectively) were found only between the ONAS test outcomes and the independent predictors pain site, and block test, respectively. In particular, post hoc analysis showed that the pain-site predictor 'cephalalgia and lower back pain' was associated with 'negative' ONAS test outcome followed by the association of 'cephalalgia and nuchal pain' and 'positive'

Table 2 Outcomes frequency distribution of the block test, ONAS test, and the PD questionnaire

Outcome	PD	ONAS		Block		Even cases	
		n	%	*n*	%	*n*	%
Negative		31	19.0	31	19.0	31	19.0
	Negative	8	4.9	8	4.9	8	4.9
	Positive	16	9.8	16	9.8	16	9.8
	Uncertain	7	4.3	7	4.3	7	4.3
Positive		132	81.0	132	81.0	132	81.0
	Negative	36	22.1	36	22.1	36	22.1
	Positive	76	46.6	76	46.6	76	46.6
	Uncertain	20	12.3	20	12.3	20	12.3

Block local anesthetic block test, *ONAS* occipital nerve applied strain test, *PD* painDETECT questionnaire

Table 3 Association analyses between ONAS test outcomes and independent predictors

Predictor	χ^2	*P* value	Post hoc cell contribution[a]	
			ONAS	
			Negative	Positive
Gender	0.311	> 0.05		
Age group	3.290	> 0.05		
Pain site	47.513	< 0.0001		
CFM				
CHZ				
CL			5.072	
CN				4.975
CNUL				
CP				
Block	163.000	< 0.0001		
Positive				12.767
Negative			12.767	
PD	1.015	> 0.05		
Positive				
Uncertain				
Negative				

χ^2 chi-square, *ONAS* occipital nerves applied strain test, *block* occipital nerves anesthetic block test, *PD* painDETECT questionnaire, *CM* cephalgia and fibromyalgia, *CHZ* cephalgia and herpes zoster, *CL* cephalgia and lower back pain, *CN* cephalgia and nuchal pain, *CNUL* cephalgia nuchal and upper limb pain, *CP* cephalgia associated with other specific pain sites

[a]Post hoc analysis results are reported as cell contribution for the reported association (the most influent two)

Table 4 Multinomial logistic regression, significant results

	Effect/predictor	χ^2	*DF*	*p*	Adjusted odds ratio			Risk[b]
					n	95% CI		
						Lower	Upper	
Model fitting (final)		59.698	12	0.000				
Likelihood-ratio								
Gender		0.471	1	> 0.05				
Age group		6.575	4	> 0.05				
Pain site		53.977	5	< 0.001				
PD outcome		0.332	2	> 0.05				
Parameter estimates[a]								
ONAS positive	Pain site CL			0.015	0.175	0.043	0.718	Decrease

CI 95% confidential intervals of the adjusted odds ratio, *CL* cephalgia and lower back pain

[a]Comparison outcomes (pain site) versus reference outcome (BUAS, positive outcome) as yielded by the multinomial logistic regression model

[b]With regard to the predictor, the risk of the considered comparison outcomes to occur versus the reference outcome (ONAS, positive) decreases when the adjusted odds ratio (and 95% CI lower and upper values) are < 1 and increases when the adjusted odds ratio (and 95% CI lower and upper values) values are > 1, respectively

Table 5 Contingency table for the accuracy analyses (sensitivity, specificity, and prior probability) of the ONAS test, against the block test and the PD questionnaire

ONAS	Block test			PD		
	Positive	Negative	Total	Positive	Negative	Total
Positive	102	30	132	96	36	132
Negative	6	25	31	23	8	31
Total	108	55	163	119	44	163
Accuracy	**%**	**CI**	***M***	**%**	**CI**	**M**
Sensitivity	94.4	90.1–98.8	4.3	80.6	73.6–87.8	7.1
Specificity	45.5	32.3–58.6	13.2	18.2	6.8–29.6	11.4
PPV	77.3	70.1–84.4	7.1	72.7	65.1–80.3	7.6
NPV	80.6	66.7–94.6	13.9	25.8	10.4–41.2	15.4

Block occipital nerve local anesthetic block, *ONAS* occipital nerve applied strain test, *PD* painDETECT questionnaire, *PPV* positive predictive value, *NPV* negative predictive value, *CI* upper and lower 95% confidence intervals expressed in percentage, *M* margin of error (one half width of 95% CI)

ONAS test outcome. Finally, 'negative' and 'positive' block outcomes were significantly and evenly associated, respectively, with 'negative' and 'positive' ONAS test outcomes.

Table 4 reports the MLR analysis results. In the latter, independent predictors were gender, age groups, pain site, and PD questionnaire outcomes; the dependent variable was the ONAS test outcome (reference outcome class, 'positive'). We found the model to fit the data significantly ($p = 0.000$), and only the pain site predictor significantly affected the outcome (likelihood-ratio tests, $p = 0.000$). To note, for the 'positive' ONAS test outcome, the predictor pain site cephalalgia and lower back pain had adjusted odds ratios (p values, 95% CI) of 0.175 ($p = 0.015$, 0.043–0.718). Therefore, the risk of testing positive with the ONAS test decreases for pain site cephalalgia and lower back pain cases.

Reliability of the ONAS Test

Sixty evaluations of 30 consecutive patients were used for the interrater agreement analysis. The latter yielded an index condition (positive ONAS test) rate of 72.5%, overall agreement of 95.0%, and Cohen's kappa of 0.875 (SE = 0.070). The latter implies excellent agreement.

For the reliability analyses, the frequency distribution of positive and negative outcomes of the ONAS test, block test, and PD questionnaire is reported as a contingency table (Table 5). The latter also details the results of the ONAS test reliability analyses against the two reference tests.

The ONAS test showed, against the PD questionnaire, relatively high sensitivity (80.6%) and PPV (72.7%) and low specificity (18.2%) and NPV (25.8%). Against the block test, the ONAS test showed high sensitivity (94.4%), PPV (77.3%), and NPV (80.6%) but lower values of specificity (45.5%).

DISCUSSION

This observational and retrospective study reports the description and reliability analysis of the ONAS test as an ON diagnostic tool. The ONAS test showed satisfactory reliability among cephalalgia patients.

ON is a cervical pain condition commonly characterized by abnormal discharges (ectopic and heterospecific) arising from putatively compromised occipital nerve structures (dorsal root, ganglion, or peripheral nerves) [8, 9]. ON pathophysiology may include 'mass effect' (nerve roots sensitization to mechanical stimuli following protracted compression); 'chemical radiculitis' (nerve roots non-cellular inflammation due to nucleus-pulposus' irritants) [29], and compression, entrapment, irritation of occipital nerves rami [4]. The aforementioned distinct mechanisms, yet not mutually exclusive, may induce maladaptive biological responses, which include "focal demyelination, intraneural edema, impaired microcirculation, Wallerian degeneration, partial axonal damage with or without neuroma and thus have the potential to generate abnormal responses from the affected nerve [30]". This study excluded patients with clinical or imaging signs of cervical hernia conditions.

ON diagnosis and management require focused history and appropriate physical examination. In 2018, the Headache Classification Committee of the International Headache Society (IHS) published the International Classification of Headache Disorders, 3rd edition [1]. According to the latter, ON diagnostic criteria, include "Unilateral or bilateral pain in the distribution(s) of the greater, lesser and or third occipital nerves and fulfilling further three criteria." The first criterion is that "pain has at least two of the following three characteristics: (1) recurring in paroxysmal attacks lasting from a few seconds to minutes; (2) severe in intensity; and, (3) shooting, stabbing or sharp in quality."

Second criterion is that "pain is associated with both of the following: (1) dysesthesia and allodynia apparent during innocuous stimulation of the scalp and or hair; and, (2) either or both of the following: (a) tenderness over the affected nerve branches (b) trigger points at the emergence of the greater occipital nerve or in the distribution of C2." The last criterion is "Pain is eased temporarily by a local anesthetic block of the affected nerve(s) [1]."

Of the above-mentioned criteria, aside from pain subjective elements reported by patients, an essential part of the diagnosis workup includes "evoking tenderness over the affected nerve branches and trigger points at the GON emergence or in the distribution of C2 [31]." The generic expression of looking for tenderness may mislead the physical exam in ON patients and hamper literature comparisons. More practical indications on exploring such tenderness may render this maneuver more precise and subject to comparison in different clinical settings. Based on the literature [6, 32, 33] and our experience, we sought to depict a practical and repeatable test based on specific anatomical landmarks to evoke tenderness in ON patients, namely the ONAS test.

The rationale for applying the ONAS test comes from both human and animal research. In the literature, "applying a strain on an injured nerve may elicit heterospecific discharges and hence subjective responses in multiple somatosensory afferents, confirming the presence of neuralgia in various clinical condition [11, 12, 14–20, 34]". This pathophysiological condition is frequent when nerve roots, ganglions, or peripheral rami are persistently inflamed or injured [8, 9].

With the ONAS test, we proposed applying a strain onto the cervical nerves along their nuchal path for several reasons:

1. The occipital nerves are easily identifiable in the nuchal area following the described ONAS test landmarks, which are highly recognized structures that are identifiable even by non-expert clinicians.
2. The occipital nerves cross solid anatomical structures at the nuchal region, which allows the strain to be adequately applied.
3. It is plausible that a strain applied onto the described specific nuchal areas would evoke abnormal subjective responses ascribable to putatively injured cervical nerves.

These factors favor the ONAS test's feasibility and efficacy.

Analyzing the ONAS test outcomes' dependence upon independent predictors might have revealed those affecting its reliability, explored domains, and content validity. In this study, ONAS test outcomes showed no significant associations with PD, gender, and age group predictors. Thus, the latter predictors did not affect the ONAS test outcomes. These findings give further support to the reliability of the ONAS test.

The ONAS test outcomes were significantly associated with the independent pain site and block test predictors. The pain site predictors 'cephalalgia and nuchal pain' and 'cephalalgia and lower back pain' showed significant associations with positive and negative ONAS test outcomes, respectively. Such findings confirm the ONAS test's ability to discern and correlate ON's presence with the patient's anatomical pain localization, even in the case of multiple pain sites.

We found significant associations between ONAS test and block test outcomes. Indeed, both tests' positive or negative outcomes were significantly and evenly associated. These results imply that the ONAS and the block tests explore similar domains, thus supporting the ONAS test's content validity. Notably, a test's "content validity comes from a strong association between the studied test and other tests that explore similar domains [35]." Moreover, the MLR analysis results additionally support the ONAS test content validity. We found that in the case of cephalalgia associated with other pain sites, particularly cephalalgia and lower back pain, the risk of a positive ONAS test outcome occurring decreases. These results imply that the ONAS test, designated to evaluate the presence of cervical nerves rami's injury and thus to uncover ON, strongly relates to congruent anatomical structures. We found no significant ONAS test outcome risk associated with the PD results. PD is a known tool to detect

NeP, as one might expect in ON presence. Although PD is appropriate as a screening tool, it should not substitute a comprehensive physical assessment [36].

The ONAS test reliability was verified, establishing its sensitivity, specificity, prior probability, and interrater agreement [26, 37]. Our study separately verified the ONAS test reliability against two reference tests: the block test and the PD. We chose the latter tests, as both are notably employed to uncover ON and NeP, respectively. To note, "sensitivity refers to the test's true positive rate, specificity refers to its true negative rate [26]". The ONAS test displayed high sensitivity and limited specificity against the PD. Against the block test, the ONAS test displayed high sensitivity (94%) and lower specificity (46%). Such results corroborate the ONAS test's capability to uncover ON in the occipital nerves' territory. The ONAS test's limited specificity suggests it is more appropriate to exclude the ON presence than confirm it [38].

This study used prior probability analysis to evaluate the ONAS test's clinical context conformity. Notably, "PPV and NPV describe the likelihood of the condition of interest, given the positive or negative test result [26]." ONAS test's PPV was $> 70\%$ against both the PD and the block test; NPV was 81 and 26% against the block test and the PD, respectively. Our prior probability findings indicate that the cohort of patients studied (i.e., cephalalgia patients) characterizes congruently the clinical context in which the ONAS test could be applied [26].

Finally, occipital nerve anesthetic block is used for ON diagnosis and treatment. It requires patient consent, sterile surgical preparation, and an adequately equipped context, which are not always available at an early stage of ON diagnostic workflow (e.g., general practitioner settings). Notably, the ONAS test, a simple and not clinically invasive maneuver, may be safely applied in every clinical context.

Study Limitations

Specialized physicians in a single pain center conducted this ONAS test reliability study. Thus, the external validity of the ONAS test still needs to be defined. It would be interesting to determine if other specialists or general practitioners, when applying the ONAS test on patients with cephalalgia, would obtain comparable results. Therefore, assessing the ONAS test's external validity requires further reliability research in diverse clinical contexts.

In this study, we did not address the therapeutic implications following ON diagnosis. It is reasonable to argue that symptom improvement following ON congruent treatment in a patient who tested positive on the ONAS test would indirectly confirm the test's diagnostic ability. Thus, future studies exploring ON therapeutic outcomes in positively tested patients may indirectly prove the ONAS test diagnostic ability.

Given the study's retrospective nature, shortage of comparative trials, and inclusion criteria for patients' recruitment, prior sample size and power analysis were not possible. Similarly, we could not prospectively assess standards for the diagnostic reliability test and analyze the receiver operating characteristic (ROC) to quantify the variability impact among individuals' decision thresholds or to develop a diagnostic prediction model. Therefore, this study conveys exploratory analyses, gathers pertinent clinical information, validates the trial context, and estimates measurement variability. Following our results, we can now arrange a further prospective study with adequate sample size, power analysis, and possibly ROC analysis and a diagnostic prediction model.

CONCLUSIONS

The ONAS test showed satisfactory reliability features among cephalalgia patients. Our results suggest it may be an appropriate early stage tool for ON diagnosis in such patients. More investigation is needed in various clinical contexts, with proper sample size and standards for reliability diagnostic tests.

ACKNOWLEDGEMENTS

The authors wish to thank the participants of the study.

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. All authors contributed to the study's conception and design. Material preparation and data collection were performed by Boaz Gedaliahu Samolsky Dekel, Maria Cristina Sorella, Alessio Vasari, and Rita Maria Melotti. Boaz Gedaliahu Samolsky Dekel performed the analyses and wrote the first draft of the manuscript; all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosures. All authors (Boaz Gedaliahu Samolsky Dekel, Maria Cristina Sorella, Alessio Vasari, and Rita Maria Melotti) declare no personal, financial, commercial, or academic conflicts of interest.

Compliance with Ethics Guidelines. The study was authorized by the University of Bologna's Teaching Hospital, (IRCCS, S. Orsola-Malpighi polyclinic, Bologna, Italy) Ethics Committee (# 235/2013/O/Oss) and conducted according to the Helsinki Declaration of 1964 and its later amendments and the International Association for the study of Pain (IASP) 's guidelines for pain research in animals and humans. All subjects provided informed consent to participate in the study.

Data Availability. The dataset generated and analyzed during the current study is not publicly available as data belong to the Bologna's University Teaching Hospital, (IRCCS, S. Orsola-Malpighi polyclinic, Bologna, Italy).

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