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Secondary Nummular Headache: A New Case Series and Review of the Literature

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Abstract

Background. Nummular headache (NH) is defined in the International Classification of Headache Disorders (ICHD) by the presence of localized pain circumscribed to a small round area of the scalp, not better accounted by any other diagnosis. As in many other primary headache disorders, secondary cases might occur. To date, 13 secondary cases have been published. We aim to present a long series of secondary NH and review the literature of symptomatic NH. **Patients and methods.** Retrospective analysis of an observational prospective cohort in a headache unit located in a tertiary hospital. We included patients that fulfilled ICHD criteria and were attributed to a secondary cause. We describe the clinical characteristics, the underlying causes, and the response to treatment. **Results.** We included 274 NH patients; eight of them (2.9%) were considered secondary. In one patient the underlying cause was subcutaneous, as for six cases the lesion was located in the bone (two hemangiomas, one osteoma, three different types of cysts), and in one was intracranial but closely related with internal diploe (cavernoma). Among our patients with secondary NH, a preventive therapy was not always needed and, when required, gabapentin or onabotulinumtoxinA were used with positive response. **Conclusions.** Secondary NH phenotype overlaps primary NH. Therefore, we recommend routine imaging study in every NH patient. Concerning treatment, it was not necessary to remove the underlying lesion to control the pain and many cases responded to the same prophylactics as primary NH cases.

Key Words: Headache Disorders; Secondary; Diagnosis; Nummular Headache; Head and Neck Neoplasms; Nervous System Neoplasms

Introduction

The International Classification of Headache Disorders, 3rd edition (ICHD-3) defines nummular headache (NH) as a primary headache disorder, in which the pain is limited to a well-circumscribed area of the scalp, either rounded (from which it takes its name, *nummus*: coin in Latin) or elliptical. Pain area is sized between 1 and 6 centimeters in diameter [1]. This clinical entity was described for the first time by Pareja et al. in 2002 [2] and since then, more than 300 cases have been described. NH incidence is estimated between six and nine cases per 100,000 inhabitants [3]. It might be underestimated, due to the lack of recognition of the condition, or its benign evolution, given that up to 18% of patients might experience spontaneous remissions [4].

The ICHD-3 states that in all primary headache disorders, other causes must be ruled out [1]. Secondary headache disorders can be related with trauma, vascular disorders, space-occupying lesions, substances, and many other different causes [1]. ICHD criteria for secondary headache diagnosis might rely on the biological plausibility and the close temporal relationship between the cause and the onset and/or the resolution of the pain [1, 5]. In

CLINICAL IMPLICATIONS

- The true prevalence of NH is unknown.
- NH might have a secondary cause.
- The clinical phenotype of the secondary NH is comparable to that of the primary NH, therefore an imaging study is recommended in all patients with NH.
- The secondary cause can be intracranial, in calvarium or subcutaneous, with similar frequency of all of them.
- Secondary NH may respond to the same treatments as primary or idiopathic NH.

the case of secondary NH, spatial relationship seems also important, and contributes to the biological plausibility.

To date, few secondary NH cases have been reported [3], although temporal relationship is not indisputable in all of them. Pathophysiology of NH remains unclear [3]. Superficial sensory fiber dysfunction has been pointed as one of the possible mechanisms [3]. As in many other conditions, secondary forms might enlighten and improve our understanding of this interesting disorder.

We aim to present a long case series of secondary nummular headache patients, describing clinical characteristics and underlying causes, and depicting the therapeutic approach, as well as the response to treatment.

Methods

This is a retrospective analysis of an observational prospective cohort. From January 2008 to June 2019, we screened all patients visiting our headache unit, and we included all consecutive cases. Inclusion criteria were: 1) Established diagnosis of probable NH according to the ICHD-3 criteria [1]; 2) Causality has been observed by one of the following: a) the headache has developed within the cause onset or the headache has resolved in parallel with the proposed cause; b) the headache is ipsilateral to the cause and in close spatial relationship with the cause.

We excluded patients with a post-traumatic NH, as this series were previously published elsewhere [4]. We also excluded patients unable to precisely describe the characteristics of the pain. All patients agreed to participate. The study was approved by the Ethics Committee for drug research of the Valladolid East Health Area.

The study took place at the Headache Unit of a tertiary hospital with a reference population of 280,000 inhabitants. This Unit receives about 800 new headache visits per year, with patients referred both from primary care and from general neurology offices.

A review of the literature was performed in PubMed, MedlinePlus, Elsevier, and Cochrane Library, reviewing all nummular headache articles, evaluating the possible secondary cases. The review comprised all published articles about NH from inception to August 2020.

Regarding the statistical analysis, we compared demographic and clinical characteristics of secondary versus primary NH patients. We employed SPSS v20.0 and used χ^2 test for evaluating association of qualitative variables, and *t*-test in the comparison of quantitative ones. We set significance level at .05.

Clinical Description

In every patient, we systematically gathered the following data at the moment of NH diagnosis: age at onset, age at diagnosis, months of evolution, and sex. We also described prior medical history, including other headache disorders or possible predisposing conditions. The clinical description included pain quality and character, temporal pattern (either continuous pain or including pain-free periods), intensity measured with a verbal rating scale (VRS) (0: no pain, 10: the worst imaginable pain), and precise location and size (in centimeters). If the patient described superimposed exacerbations, we recorded their quality, characteristics, duration, and intensity. All patients were carefully examined, paying special attention to the presence of hypersensitivity in the emergence point of every pericranial nerve, in order to exclude pericranial neuralgias in the differential diagnosis. The presence of localized allodynia in the area of NH, or in other cranial regions, was considered upon physical examination. We analyzed the presence of other signs of sensory dysfunction (hyperesthesia, hyperalgesia, hypoesthesia), and other associated symptoms such as photophobia, phonophobia, nausea, vomiting, trigeminal autonomic symptoms/signs, and worsening with physical activity.

We systematically requested cranial imaging in every NH patient, either magnetic resonance imaging (MRI) (44.6% of patients) or computerized tomography (CT) (55.4%); in this study, we analyze and describe the presence of any abnormality. In all the images, the location of the lesion was described, both in the parenchyma window and in the bone window. We present the images by indicating the location of the cause and the headache location.

Concerning treatment, we described prior use of acute and preventive medications, as well as the response to them. The response to treatment was collected through clinical interviews with the patient, who recorded the headache days per month on a daily calendar. Response to preventive was defined depending on the decrease in number of headache days per month, compared with the month preceding the treatment onset. Response was defined as optimal if decrease of headache days per month was 75% or higher, positive if decrease was between 50% and 74%, partial if it was between 30 and 49%,

and no response if it was below 30%. Symptomatic medication response was defined as optimal if pain freedom within 2 hours occurred in >75% of the utilizations, positive if it occurred in 50–74% of the utilizations, partial if it occurred in 30–49%, and no response if frequency of response was lower than 30%. We describe follow-up of the patients, defining spontaneous remission if patients remained completely pain-free during at least 6 months without any therapeutic intervention.

We present qualitative data as frequency and percentage. Quantitative data are presented as mean and standard deviation (SD) if the distribution was normal, or median and interquartile range (IQR) if the distribution was not normal.

Results

During the study period 6470 patients were attended in the Headache Unit, 274 patients have been diagnosed with NH and eight patients (five of them female), have been diagnosed with secondary NH (0.12% of all patients attended and 2.9% of the patients with NH diagnosis). Mean age of onset was 50.0 ± 20.1 years (range: 17–84). Table 1 summarizes demographic and clinical data. Table 2 summarizes the employed treatments and the clinical response. Figure 1 shows the imaging studies pointing the cause and the symptomatic area.

Case 1: A 51-year-old male with previous ischemic heart disease treated by coronary artery bypass. From 2 years before, he reported pressing, continuous pain, rated as 6 out of 10 in VRS, located in the left occipital scalp, in a circular area of 5 centimeters, with neither exacerbations nor other associated symptoms. Upon the examination, localized allodynia was present.

The cranial CT showed a $2 \times 2 \times 2$ centimeters rounded subcutaneous mass, with sharp edges, without radiological signs of malignancy. Lesion topography coincided with the painful area. Radiological appearance was suggestive of fibroid or sebaceous cyst.

The patient was initially treated with gabapentin 400 mg BID and amitriptyline 25 mg QD, with no response. He finally received onabotulinumtoxinA (onabotA), 25 units divided into five points in the painful area [6], with optimal response while the lesion was still present in follow-up CT scans.

Four years after the first study, a new CT showed that the aforementioned lesion had resolved, with only a small scar visualized in the area, suggesting an infective or inflammatory etiology.

Case 2: A 60-year-old male patient with history of smoking habit and episodic tension type headache. In the previous three years, he described a new and different headache, consisting of pressing, continuous daily pain, rated 5 out of 10 in intensity, and located in the right parieto-temporal junction, in a well-defined circular area of three centimeters diameter. The patient described superimposed exacerbations rated 7 out of 10 on VRS lasting around 5 minutes. Upon examination, he presented with hypoesthesia in the painful area, along the right temporo-parietal suture.

CT showed a well-defined, circumscribed osteolytic, isointense to cerebrospinal fluid lesion, suggestive of arachnoid granulation, and coincident with the nummular area.

The patient was treated with onabotA, 12.5 units divided across five points, repeated quarterly. Response was optimal after 12 months, then onabotA was discontinued and the patient is still asymptomatic after 24 months of follow up.

Case 3: A 54-year-old male patient was referred to our unit because of localized pain for the previous six months. The pain was described as burning, intermittent, and occurring one to five times per day, with two or three seconds duration, and rated 8 out of 10 in intensity. Pain was circumscribed to a left parietal circular area of two centimeters m diameter, with no pain elsewhere. Local and neurological examination was normal.

Cranial CT showed a lytic lesion in the calvarium, measuring $1.1 \times 0.4 \times 0.4$ centimeters, without internal or external table disruption or expansive character. Radiological appearance suggested bone hemangioma.

The patient described inadequate response to symptomatic therapy with paracetamol or different nonsteroidal anti-inflammatory drugs (NSAIDS), and partial response to metamizol. He was treated with onabotA, injecting 25 units across 5 points with an optimal response after 24 months of follow-up.

Case 4: A 58-year-old woman with no relevant medical history, was referred due to three-four a day pain paroxysms during the previous three months. The quality was described as burning, with intermittent episodes, lasting up to 2 minutes, with 5/10 intensity, and located in the left parietal scalp, in a circular area of 5 centimeters in diameter. The examination revealed allodynia upon the symptomatic area.

Cranial MRI showed an intradiploic lesion in this location, slightly expansive, with integrity of the cortical and without intra or extracranial expansion; with a well-defined shape and internal trabeculae, and measuring $3 \times 2.5 \times 8$ centimeters. Radiologic diagnosis was suggestive of bone hemangioma.

The patient did not request preventive therapy because of the mild and infrequent nature of pain.

Case 5: A 19-year-old woman was referred to our unit, due to a 2-year history of pressing intermittent episodes of pain, occurring up to four times per day, rated 4 out of 10 in intensity, and of 1 minute duration. They were located in the right occipital scalp, in a five centimeters circular area. She denied associated symptoms. Neurological examination was normal, without sensory disturbances or tenderness of occipital nerves.

Cranial MRI revealed a bone lesion between internal and external tables in the painful area, measuring

Table 1. Summary of our case series of secondary NHs: demographic and clinical data

Item/Case	1	2	3	4	5	6	7	8
Age at onset	49	57	54	58	17	52	29	84
Months of evolution	24	36	6	3	24	36	24	20
Sex	M	M	M	F	F	F	F	F
Prior headache	No	TH	No	No	No	No	No	No
Pain quality	Pres	Pres	Burn	Burn	Pres	Pres	Burn	Stab
Pain pattern	Cont	Cont	Interm	Interm	Interm	Cont	Interm	Cont
Presence exacerbations	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intensity (0–10)	6	5	8	5	4	4	6	3
Location	O	P-T	P	P	O	F	P	T
Side	L	R	L	L	R	L	R	L
Diameter (cm)	5	3	2	5	5	4	2	5
Shape (Circ/oval)	C	C	C	C	C	C	C	C
Sensory disturbances	+	+	−	+ AL	−	−	−	−
Presence of nausea, vomiting, photo/phono/osmophobia or cranial autonomic symptoms	No	No	No	No	No	No	No	No
Cause	Fibroid, sebaceous cyst	Arachnoid granulation	Bone hemangioma	Bone hemangioma	Cholesterol cyst	Osteoma	Cavernoma	Angiomatous area or initial Paget

TH=Tension-type headache; Circ=circular; O=oval; CONT=continuous; STABB=stabbing; PRES=Pressing; AL=Allodynia; F=Frontal; P=Parietal; T=Temporal; O=Occipital, Vx=Vertex; R=Right; L=Left; S=Sagital.

$0.7 \times 0.7 \times 1.5$ centimeters, and suggestive of cholesterol cyst.

Preventive treatment was offered but the patient declined it. A spontaneous remission was achieved 17 months after the pain onset, and patient remains asymptomatic after 80 months of follow-up.

Case 6: A 55-year-old woman with prior medical history of hypertension, type 2 diabetes mellitus, and breast cancer treated with surgery 12 years earlier, with no evidence of relapse. A right parietal meningioma was resected 7 years previously. During the 3 years prior to referral, she complained about pressing and persistent pain, with 4/10 intensity, located in the left frontal scalp in a rounded area of 4 centimeters diameter. The patient described exacerbations every other day, of burning quality and 7/10 intensity.

Cranial CT revealed a well-circumscribed, 12 millimeters, hyperdense mass, inside the frontal sinus corresponding to the painful area suggestive of frontal osteoma.

The patient described lack of response to paracetamol or NSAIDs. She received gabapentin 400 mg three times a day for 3 months, with optimal response, that persisted once the treatment was stopped. The patient remains pain-free after 8 years of follow-up.

Case 7: A 31-year-old woman with a history of strabismus treated with surgery. At age 15, she began to experience seizures, with response to low doses of valproic acid. For a year prior to referral, she complained about burning pain occurring twice a week, lasting around 10 minutes with 6/10 intensity. The pain was located in the right parietal region, circumscribed to a two centimeters rounded area. Neurological examination was normal.

Cranial MRI revealed a $1.4 \times 0.8 \times 1.1$ centimeters diameter cortico-subcortical lesion in the right parietal lobe of irregular borders, surrounding by a hypointense halo, and with a center with heterogeneous signal (hyperintense in sequences enhanced in T2 and iso/hypointense in T1 sequences). Radiological diagnosis was cavernoma.

As preventive treatment, a substitution of valproic acid for carbamazepine 200 mg three times a day was proposed with optimal response for both seizures and nummular pain. Response to treatment persists after 34 months of follow-up.

Case 8: An 84-year-old woman, with prior medical history of high blood pressure, asthma, generalized anxiety syndrome, peripheral vertigo, and prior fractures of the hip, humerus, and knee.

Twenty months prior to presentation, she experienced new-onset continuous stabbing pain, in left temporal region, confined to a circular area of 5 centimeters diameter. Pain was rated as 9 out of 10. After 3 weeks, pain spontaneously improved, with a basal pain intensity of 3/10 and superimposed exacerbations twice a day. Brain MRI showed a 2 centimeters abnormality, in diploic area in the left temporal region, without a clear lytic lesion, suggesting angiomatous change or early Paget's disease.

The patient was treated with amitriptyline 10 mg daily with an optimal response after 20 months of follow-up.

Discussion

In the present article, we aimed to describe demographic, clinical characteristics and therapeutic response in the largest series of secondary NH cases published up to date. NH is a primary headache in which the

Table 2. Employed treatments and clinical response in the present series of cases

Case	Age of onset	Sex	Treatment	Response to treatment	Duration of follow-up (months)	Evolution
1	49	M	Gabapentin 400 mg/12 hours Amitriptyline 25 mg/24 hours	No response.	48	Optimal response with OnabotA. Spontaneous disappearance of the subcutaneous lesion.
			Lidocaine anesthetic blocks of the left major occipital nerve	Partial response lasting 3 or 4 months.		
			OnabotA 25 U in 5 points	Optimal response		
2	60	M	OnabotA 12.5 U in 5 points	Optimal response	24	Disappearance of pain.
3	54	M	Paracetamol 1.000 mg or NSAIDs/8 hours	No response	24	Optimal response with onabotA.
			Metamizol 575mg/ 8 hours	Partial response		
			OnabotA 25 U in 5 points	Optimal response		
4	58	F	Did not require treatment		3	Clinical stability.
5	19	F	NSAIDs/8 hours	Optimal response	80	After 17 months from the beginning, pain remitted spontaneously.
6	55	F	Paracetamol 1.000 mg or NSAIDs/8 hours	No response.	96	She was kept on gabapentin for a few months and was gradually withdrawn, remaining asymptomatic without medication after 8 years of follow-up.
			Gabapentin 400 mg/ 8 hours	Optimal response		
7	31	F	Carbamazepine 200 mg/ 8 hours	Optimal response	80	After 17 months from the beginning, pain remitted spontaneously.
8	83	F	Amitriptyline 10 mg/24h	Optimal response	20	She presented an optimal response with amitriptyline 10 mg daily after 20 months of follow-up.

pathophysiology remains unknown. As in many other conditions, secondary cases may shed light on the underlying etiology of this disorder.

In our sample, 274 patients were diagnosed with NH, of which 8 cases (2.9%) were classified as secondary NH, corresponding to an estimated prevalence of 0.26 cases per 100,000 patient-years. Since its description, 350 cases of NH have been described in articles worldwide [3, 7, 22–24], among which 13 cases (4.2%) were deemed secondary [8–18]. Combining our figures with those that were previously published, secondary NH cases comprise 21 (5.5%) of reported NH cases.

Table 3 summarizes demographic and clinical features of previously described NH cases.

The ICHD states that a headache can be secondary to a certain cause if there is biological plausibility, and if the onset or resolution of the event is related with the onset or resolution of pain [1]. In the case of NH topographical relationship is probably also important to determine the biological plausibility.

Both in the previously published cases and in our series, almost all the described patients exhibited close anatomical relationship between the pain and the lesion. This might suggest that superficial sensory fibers and trans-sutural nerve terminations could explain the extracranial manifestation of pain caused by intracranial conditions [21].

From the topographical point of view, secondary NH can be classified depending on the lesion site into intracranial, located at the calvarium or subcutaneous, with a similar frequency of reported cases. To date, taking into account the published cases of secondary NH and our series, seven patients had NH secondary to intracranial lesions: two arachnoid cysts, two supraselar tumors, one meningiomas, one cavernoma, and one pituitary adenoma. Seven patients had lesions located in the calvarium: two intraosseous hemangiomas, two osteomas, one case of craneosynostosis, one case of hyperostosis, and one subarachnoid granuloma. Subcutaneous lesions were responsible for NH in seven patients: two cases of eosinophilic granuloma, two subcutaneous aneurisms, subcutaneous hematoma, subcutaneous cyst and squamous carcinoma [8–18]. Figure 2 depicts the different locations of secondary NH causes and the reported cases.

We have not included post-traumatic NH in the secondary NH group, as these patients do not have an underlying "physical" etiology, and trauma could precipitate NH by damaging superficial nerve fibers [4]. This case series is discussing secondary causes with an underlying mass lesion. Similar to secondary NH, patients with posttraumatic NH may have a close spatial relationship with the area of pain from the head injury. A recent study from our group published a series of 29 patients with posttraumatic NH, what would account for

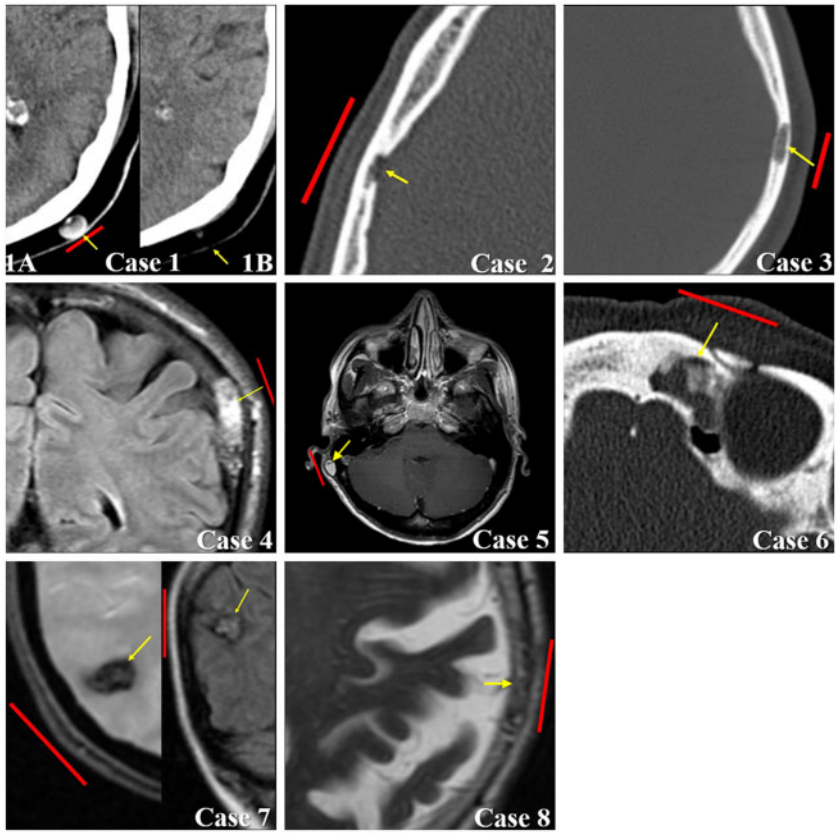

Figure 1. Case 1: (A) Initial cranial CT, where a small subcutaneous mass can be seen in the left occipital region that suggests fibroma, sebaceous cyst, fatty necrosis or pilomatrixoma. **Case 1:** (B) Follow-up cranial CT 4 years after, where it is observed that the lesion has completely disappeared, only a small scar being visualized in the area of the subcutaneous injury. **Case 2**. Axial slices of cranial CT in which arachnoid granulation is suggested in right temporoparietal region, also shows an arachnoid cyst in in left temporal pole. **Case 3**. Cranial CT suggested bone hemangioma in left parietal bone as the first possibility. **Case 4**. Brain MRI showing an intradiploic lesion in left parietal tuber suggesting bone hemangioma. **Case 5**. Cranial MRI, a bone lesion was observed between the internal and external tables in right occipital, measuring $0.7 \times 0.7 \times 1.5$ cm, suggestive of residual protein or cholesterol cyst. **Case 6**. Cranial CT showing a suggestive image of left frontal osteoma. **Case 7** Brain MRI in axial T2 and coronal T2 flair sections suggesting right parietal subcortical cavernoma. **Case 8**. Brain MRI in axial T2 showing an alteration in the diploe signal in the left temporal region in a segment of 2 cm, without a clear lytic lesion, suggesting an angiomatous area or initial Paget's disease.

12.8% of the total number of NH patients. In that series, posttraumatic NH patients presented an older age at onset and more frequent allodynia than idiopathic NH patients as the sole differences [4]. This could suggest that focal trauma triggers superficial sensory dysfunction in those patients. Posttraumatic NH could be an example of a possible individual predisposition, considering the relative rarity of the disorder when compared to the many mild or moderate cranial traumas most humans experience.

Idiopathic NH typically starts in adulthood, around 49.6 ± 18.3 years [4], with a similar age of onset in all the secondary cases (including those in this article), 48.9 ± 16.7 years. Gender distribution shows female predominance in 64.4%, and a more balanced distribution in secondary ones (57.1% females), taking into account the cases reported in the literature and those presented in this article. Mean time of evolution since onset to diagnosis was 28.4 ± 63.2 months in idiopathic cases and 21.6 ± 12.1 months in the present secondary NH series [4].

Clinical presentation of secondary NH was similar to the published primary series: pain quality was also mainly pressing (50% vs 42.7%) followed by burning (37.5% vs18.3%) and stabbing (12.5% vs 17.4%). Mean intensity was also similar (5.1 ± 1.5 vs 5.2 ± 1.6), parietal was the most frequent location in both cases (40% vs 31.2%), mean diameter was comparable (3.9 ± 1.4 vs 4.4 ± 1.3 cm) and frequency of allodynia upon examination was lower in secondary NH (12.5% vs 35.3%) [4]. None of our patients had prior history of migraine and typical migrainous symptoms such as photophobia, phonophobia, nausea, orthostatic component of the headache or preference for lying down during attacks (clinophilia) were absent in our series. Our patients also did not present cranial autonomic symptoms.

When comparing epidemiological characteristics between primary and secondary NH cases, we did not find

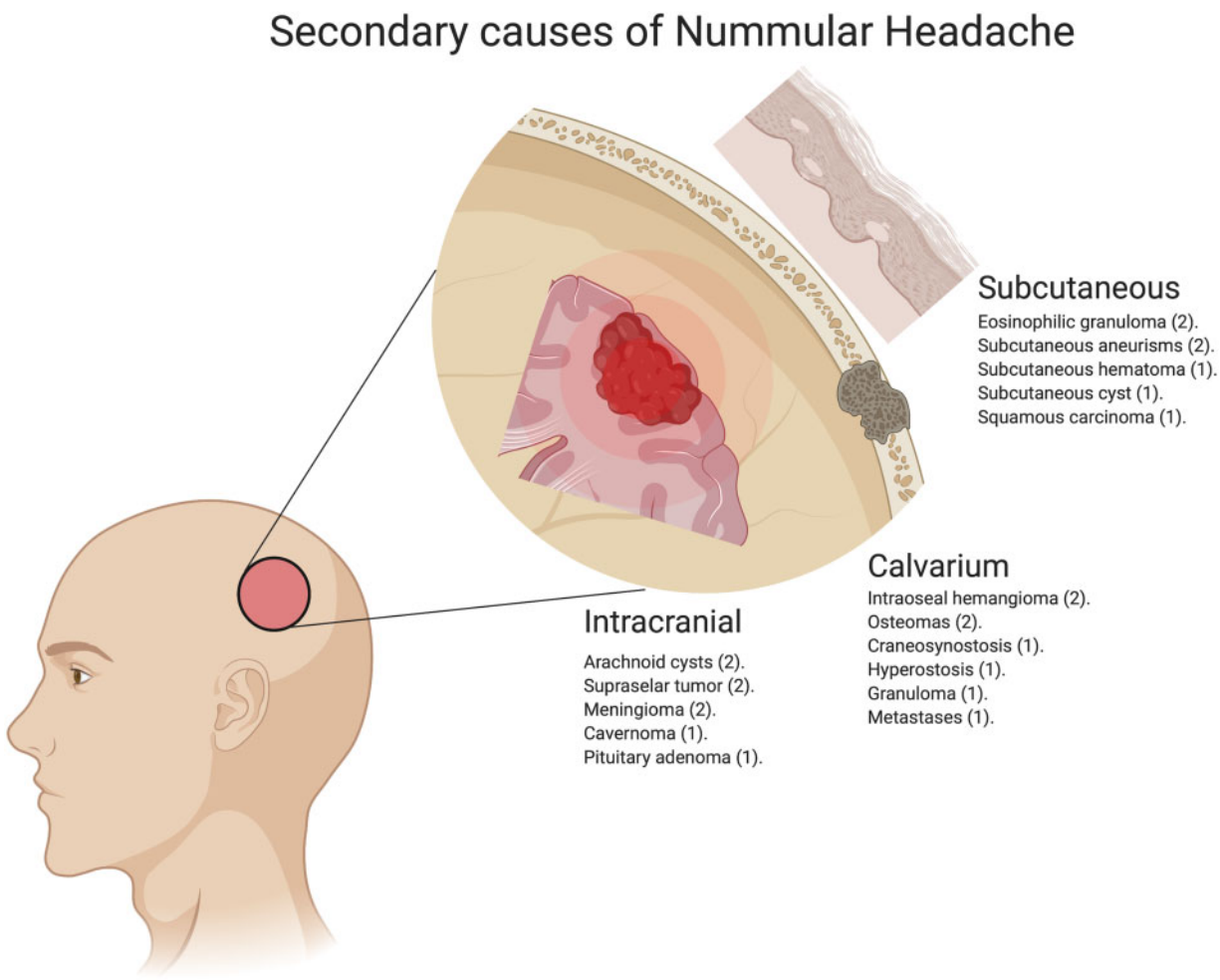

Figure 2. Causes of secondary NH depending on the location and number of reported cases per sub-type.

differences regarding age at onset and gender. There were also no differences between the two groups in the time of evolution, or in the presence of exacerbations. Table 4 shows the comparison of the basic demographic and clinical variables of primary NH and secondary NH, including their *P* values.

In our series, background pain intensity was 5.1 points on VRS scale, ranging from 3 to 8. Only a third of previously published secondary cases report pain intensity, which ranges from 3 to 8 out of 10. In the largest case series, an average pain intensity of 5.7 was observed, in line with our results [3]. When considering superimposed exacerbations, they were present in 70% of our secondary NH patients, within the realm of previous series of secondary NH (53.8%) [8–18]. In the largest case series of idiopathic NH, 58.8% of patients reported superimposed exacerbations [19].

Regarding symptomatic treatment, 10% of our patients had a positive response to paracetamol and 10% to NSAIDs. This percentage was lower than that described in primary cases (32.1%) [4]. In our series, an optimal response was obtained in 30% of cases with oral preventive medication (gabapentin, carbamazepine and amitriptyline). In previously published secondary NH cases, preventive medication was needed in 37.5%, with a positive response in 44.4% of cases. Table 3 summarizes the response to treatment in the previously published cases. Response rate in primary cases is present in about 67.7% of patients [4], with the most frequently used drugs including gabapentin, lamotrigine, amitriptyline and pregabalin [4, 10]. OnabotulinumtoxinA appears to be another favorable option with more than 77% of idiopathic NH patients experiencing a 50% response [6]. In our series of secondary NH, optimal response with onabotA occurred in three out of four cases, and partial response in the remaining case, whereas in the previously reported secondary NH cases, onabotA was never employed. Concerning surgery, in the previously reported cases, 46.2% of patients described pain cessation after surgical removal of the lesion [9, 11, 14, 17, 18]; in many cases and in our series medical management alone was sufficient. Randomized controlled trials are needed to definitively determine the role of preventive agents in this setting.

Table 3. Employed treatments and clinical response in the previously reported secondary NH cases

Authors	Age of onset	Sex	Associated injury	Treatment	Response to treatment	Duration of follow-up (months)	Evolution
Guillem et al. 2007 (n=1)	60	F	Meningioma	Resection of the meningioma		Asymptomatic	24 Asymptomatic
Guillem et al. 2009 (n=2)	52	F	Arachnoid cyst	Gabapentin, indomethacin, amitriptyline	No response	48	Without changes. She did not want to try botulinum toxin or surgery.
	36	F	Arachnoid cyst	Paracetamol, metamizole and ibuprofen	No response	36	Moderate improvement with pregabaline 75 mg/day
Álvaro et al. 2009 (n=2)	65	M	Protruding lesion, specula shaped, with the bone layer preserved	Metamizole, indomethacin, and NSAIDs	No response	?	?
				Local infiltration with lidocaine	Partial		
				Amitriptyline, gabapentin, and oxcarbazepine	No response		
	72	F	Empty sella (pituitary adenoma was removed by a transsphenoidal approach)	Indomethacin, NSAIDs, amitriptyline, gabapentin and valproic.	No response	?	?
Chui et al. 2013 (n=1)	53	F	Nonfunctional oncocytoma at suprasellar region	Resection	Optimal	72	Asymptomatic
Yin et al. 2013 (n=1)	52	M	Resection for pituitary prolactinoma	Gabapentin 300 mg/day.	Optimal	24	Asymptomatic without treatment
			trans- sphenoidal approach	Resection	Optimal		
Ulivi et al. 2014 (n=1)	42	F	Calcified hematoma in epicranial tissues	Ibuprofen and ketoprofen	Positive.	?	Spontaneous remission headache
López- Mesonero et al. 2014 (n=1)	40	F	Bone deformities in relation to surgery and craniosynostosis	Patient refused any treatment.		?	?
López-Ruiz et al. 2014 (n=2)	42	M	Fusiform aneurysm 2.5 cm in diameter in superficial temporal artery	NSAIDs, lamotrigine, gabapentin, beta-blockers and topiramate.	Poor response.	8	Asymptomatic
				Zolmitriptan	Partial		
				Resection	Optimal		
	56	M	9 mm aneurysm in right middle cerebral artery bifurcation	NSAIDs and local anesthetic injections.	No response	?	Aneurysm embolization was proposed, but the patient preferred conservative management.
				Zolmitriptan and sumatriptan	Poor response		
Silva-Rosas et al. 2017 (n=2)	35	M	Eosinophilic granuloma (histiocytosis)	Resection	Optimal	60	Asymptomatic
	12	M	Eosinophilic granuloma (histiocytosis)	Resection	Optimal	6	Asymptomatic

In some series [4], almost 20% of patients with idiopathic NH experienced spontaneous remissions. A priori, this percentage should be lower in secondary NH patients, given the presence of a persistent underlying cause. Pooling all the secondary NH cases described to date, spontaneous remissions occurred only in 8.7% cases.

Treatment resistance and progressive worsening of headache are considered red flags of secondary headaches [25]. Three percent of all NH patients in our series

Table 4. Comparison of the basic demographic and clinical variables of primary NH and secondary NH, including their *P* values

	Secondary NH	Primary NH	*P*-value
Age of onset	50±20.1	52.3±17.9	.7
Gender	62.5% female	65% female	1
Months of evolution	21.6±12.1	31±70.8	.16
Exacerbations	87.5%	46.2%	.15

were found to have a secondary cause. The phenotypes of primary and secondary NH do not differ significantly, and secondary causes include easily treatable entities (Paget's Disease) and ominous causes (multiple myeloma, metastasis) that should not be missed. Thus, it should be recommended to consider cranial imaging in every case. Special attention should be paid to the painful area and bone window should also be examined, as many causes might be unnoticed. In more than a third of secondary NH cases (43.5%), the lesion was located into the calvarium [8–14, 17, 18].

Temporal relationship with the onset of the cause seems also important in order to establish causality, though in this type of headache this relationship is commonly impossible to determine. Moreover, headache duration before consulting should be lower in secondary NH than in idiopathic NH cases, as an underlying lesion is expected to compromise more quickly the affected nerve fibers and/or cause additional symptoms. However in previously reported idiopathic NH latency between onset and diagnosis was 28.4 ± 63.2 months [4], whereas in our secondary NH cases this latency was 21.6 ± 12.1 months. This could be explained by the relatively mild nature of pain in NH, with moderate intensity and low need of acute medication.

In practice, one of the aspects of greatest clinical importance is the presence of warning signs or "red flags" of headaches. Several authors recommend the use of the systematic list SNNOOP10, and propose different "red flags" to identify headaches with secondary causes. In our series, the red flags that were presented were a history of malignancies, (though not related with the lesion causing the headache) (12.5%), onset after 65 years (12.5%), change of pattern or recent onset of new headache (100%) and atypical presentations (100%). These results support the use of the SNNOOP10 list because all the cases presented at least one of the red flags included in the list [25].

Pathophysiology of NH is still under discussion, though a peripheral origin seems more likely, based upon: a) the description of decreased pressing pain thresholds restricted to the painful area [16], b) the highly localized pain in the absence of headache in other territories, with focal sensory dysfunction signs upon examination, c) the significant improvement achieved with very low doses of onabotA in most patients [6], and d) the absence of typical migraine symptoms in most of the cases.

An intracranial lesion can lead to a pain as NH due to the transmission from meningeal nociceptors to the extracranial collaterals of meningeal nerves that cross the calvarium and activate in the vicinity [20]. The close spatial relationship in most of the described secondary NH cases would support this hypothesis.

Our study has some important limitations: it is a single center study with a relatively small sample size. Considering temporal relationship, in none of our patients surgery was required, so the response after surgical removal of the underlying lesion was not verified. Pathological confirmation was missing in our patients, with the final diagnosis based on imaging. Since headache is extremely prevalent, it can occur simultaneously with another disorder by chance and without a causal relation. Finally, primary NH pain is generally mild and benign, so the probability that general practitioners or general neurologists refer these cases to a tertiary hospital (or a Headache Unit) is low. Strengths of our study are the long term follow up of most patients (with no subsequent modification of the diagnosis in any patient) and the use of the same protocol as in idiopathic NH, making it possible to compare clinical characteristics of patients.

It is necessary to deepen the study of secondary NH and report more case series to elucidate the pathophysiology of the disorder and the optimal management of patients.

Conclusion

This series brings the number of published secondary NH cases to 21, comprising 5.5% of all published NH cases. The causes of secondary NH in these cases were located intracranially, in the calvarium, or subcutaneously. Demographic and clinical characteristics of secondary NH were comparable to idiopathic cases. In many cases, adequate response to treatment avoided surgical removal of the lesion. Response to treatment was comparable to primary NH.

LIST OF ABBREVIATIONS:

NH: nummular headache.
ICHD-3: International Classification of Headaches.
VRS: Verbal Rating Scale
MRI: magnetic resonance imaging
CT: computerized tomography.
SD: standard deviation
IQR: interquartile range.
BID: twice daily.
QD: once daily.
Mg: milligrams
OnabotA: OnabotulinumtoxinA
NSAIDS: non-steroidal anti-inflammatory drugs

cm: centimeters
F: female
M: male
R: right
L: left
ML: middle line.

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