Journal of Integrative Neuroscience

J. Integr. Neurosci. **2022**; 21(6): 166
https://doi.org/10.31083/j.jin2106166

Review

Cranial Autonomic Symptoms and Migraine: What Relationship and What Meaning? A Review

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Academic Editor: Rocco Salvatore Calabrò
Submitted: 23 June 2022 Revised: 22 July 2022 Accepted: 22 July 2022 Published: 9 October 2022

Abstract

Cranial autonomic symptoms (CAS) have been usually associated with trigeminal autonomic cephalalgias (TAC's), however in the last few years several reports in adult and pediatric population have reported important presence of the CAS in migraine. Also several evidences experimentally show that the increased parasympathetic outflow can enhance the sensitization of nociceptive receptors involved in migraine. The presence of CAS suggests an activation of the trigeminal-autonomic reflex, probably related to an over-activation of the trigeminal afferent arm. For these reasons identifing and understanding of these symptoms in migraine may be important to help in the diagnosis and effective management. The purpose of this review is, analyzing the literature data, to discuss the prevalence of these CAS in migraine, the pathophysiological meaning in the pathogenesis of migraine and whether their presence influences the prognosis and therapy of migraine in adult and pediatric age.

Keywords: migraine; cranial autonomic symptoms; parasympathetic system; children; adult; trigeminal autonomic cephalgias

1. Introduction

Migraine is a highly disabling disease both in childhood and adulthood, it is one of the three more disabling diseases according to the WHO [1]. It presents a wide heterogeneity of clinical manifestations, however in the light of the diagnostic criteria, established by the IHS [2], are mainly based on certain requirements: recurrence of attacks, established duration of attacks, characteristics of pain, involvement of the general autonomic system (nausea and/or vomiting), intolerance of sensory channels (photophobia, phonophobia and possibly osmophobia) and in a subgroup of subjects an altered excitability of the cortical and subcortical structures may determine several varied neurological manifestations gathered in the definition of migraine aura. These clinical characteristics obviously underlie the involvement of defined anatomofunctional systems, as well as neurochemical and hormonal systems, and furthermore their presence or absence can influence the treatment and the long-term prognosis. More recently, another clinical aspect of migraine, extensively studied, is the allodynia [1] which appears to influence both the response to acute treatment and the prognosis of migraine sufferers [1]. In relation to the main characteristic of pain, the major invoked pathophysiological mechanism is the trigemino-vascular reflex. It activates a sort of sterile inflammation by the trigeminal fibers that innervate the intra and extracranial vascular structures (rich in painful innervations), provoking the onset of migraine pain [1]. In contrast to the trigemino-vascular reflex as a determinant of migraine pain, the so-called trigemino-autonomic reflex is opposed because the trigeminal fibers, activated by cortico-subcortical structures, would activate the cranial parasympathetic autonomic fibers to determine the appearance of cranial autonomic symptoms that distinguish a group of well-defined headaches (the trigeminal autonomic headaches called TACs, group III of the IHS Classification [2]) which, despite having some different characteristics, are united by their strict unilaterality and by the cranial autonomic symptoms (CAS). The IHS classification [2] identifies CAS as the following symptoms: lacrimation, conjunctival injection, rhinorrhea, nasal congestion, forehead and facial sweating, ptosis, miosis and eyelid edema. This clear clinical and clinical physio-pathological distinction between migraine and TACs has actually been partly questioned in the last 20 years, both because the TACs themselves, especially Cluster Headache, have clinical characteristics of migraine in many patients [3] and because since 2002 a series of papers have been published both in adult and developmental migraine populations which demonstrated the presence of cranial autonomic disorders (CAS) in a moderate proportion of migraine sufferers [4–28]. Furthermore, some studies have suggested that the response to treatment and prognosis could be influenced by their presence [5,10,29–35]. The purpose of this review is a careful examination of the papers published on the presence of these symptoms in migraineurs, on the possible pathogenetic mechanisms involved and on their possible clinical significance.

2. Clinical Summary

A migrainous patient has always been described with a multiform complex heterogeneous clinical phenotype of his attack, starting with the multiple prodrome, followed by the aura with involvement of different cortico-subcortical areas, continuing with the painful attack characterized by several local and general symptoms to conclude with the postdromes [1]. However, the attention of clinicians and researchers have mainly focused on the some guiding symptoms useful for diagnosis, for treatments and for neurophysiological-functional studies [2]. This simplification has underestimated the clinical richness of the migraine phenotype with the potential danger of including in a single diagnostic category subjects with different pathophysiological mechanisms and different prognosis.

CAS have long been underestimated [34], even if they had often been described [36], in fact the first studies [4–8,12,13] showed that they were present during the attack in a large proportion of migraine sufferers, both pediatric and adults.

2.1 Epidemiological Point

After the first clinical studies [4–6] that showed the good prevalence of CAS during migraine attack, Obermann *et al*. [7] conducted an epidemiological study on the presence of unilateral CAS in the adult general population which found a prevalence of 25.2% of them (ratio M/F 1:2), more than 50% had at least two CAS, in which conjunctival injection and tearing were more represented. In addition, CAS were more frequently associated with unilateral headache and more severe pain attack, than those who didin't have these symptoms. Very recently the Danish group's study [28], conducted on population, reported prevalence of 57% of CAS (at least one CAS) and 31% with two or more CAS by a questionnaire while the prevalence reduced to 44% of one CAS and 22% with two or more CAS by semi-structured interview. The facial/forehead sweating was the most common symptom (39%) followed by lacrimation (24%). They reported weak correlation between symptoms and no clear clustering of them.

These data [7,28] confirmes those coming from the clinical series [4–6,8–15,17–27]. Further the prevalence may be sometimes undervalued because some researches only look for the unilateral CAS while in clinical series they may be also present bilaterally as well as migraine pain may have bilateral lateralization. In Table 1 the studies [7,16,28] on population are summarized.

Clinical studies show an obvious higher prevalence of CAS up to over 70% due to case selection, however in the clinical experience the CAS are often not reminded (maybe are mild), if not focused the attention, and that can probably explain the great variability of data and also the reported prevalence below 3.2% in Turkish database [16], as the same authors suggest. Danish researchers propose that future studies must include subjects with at least two CAS to define CAS migraine+. The prevalence of unilateral CAS varies between % in adults but several studies report that CAS occur bilaterally. The prevalence in women is confirmed and chronic migraine has often a higher prevalence of CAS than episodic migraine. In Table 2 [4,6,8,11,15,17,18] and Table 3 [17–20,22–26], the clinical series of adult migraineurs are summarized.

There are only 4 studies conducted in pediatric age, they don't show a predilection for female sex (in prepuberal age male/female ratio is about equal in migraine), but the prevalence is in a range between 40% and 67% moreover they are present in about 50% of children under seven years, often bilaterally. Pediatric studies [12–14,21] are summarized in Table 4 (Ref. [12–14,22]).

2.2 Clinical Point

The diagnostic criteria of the IHS classification [2], used in the TACs, identify the following signs/symptoms as an expression of the autonomic trigeminal reflex: lacrimation, eyelid edema, conjunctival injection, nasal congestion, rhinorrhea, face and forehead sweating, eyelid miosis and ptosis. These CAS are those usually searched in studies on migraines, however several authors have researched and proposed other symptoms in consideration of the parasympathetic/sympathetic innervation involved in the head, which are frequently present and often associated with others [12–14,26]. Those reported are red ear, facial flushing, foreign body sensation in the eye, aura fullness, and most recently throat swelling and voice change. Fig. 1 illustrates the different signs/symptoms, reporting the range of prevalence of each single sign in the literature.

The prevalence of the single cranial symptom is variable in literature and probably depends on various factors. In general lacrimation and forehead/facial sweating are most represented, while myosis and ptosis are the least present (see Tables 1,2,3 and Fig. 1). It is probably due to easier recognition of the parasympathetic activation (lacrimation, conjunctival injection) compared to sympathetic hypoactivity (ptosis) by the migraineurs. We may affirm that often at least 50% of CAS+ migraine sufferers report more than one CAS in the course of an attack.

There is no particular difference between the pediatric and adult age, this data leads us to think that this phenotype is part of the pathophysiological aspect of these migraine sufferers and it does not appear related to the worsening of the disease in duration or severity of attacks because it is already present in a proportion of children under 7 years [14]. Certainly further prospective studies on a larger population are needed to clarify this important aspect.

Although different topographical areas of the head are involved (eyes, face, nose, ears, etc.) and functional areas of the autonomic control of the head (secretory, vasodilatory, sympathetic, etc.), the studies carried out fail to highlight a mode of association between them or a tendency to form specific clusters even if some authors favor these hypotheses [13,20] while the most recent Danish study [28] does not support these conclusions.

Table 1. Migraine with cranial autonomic symptoms, studies on general population.

Authors (ref no.)	M. Oberman *et al.* 2007 [7]	D. Uluduz *et al.* 2016 [16]	CG Christensen *et al.* 2022 [28]
Cases	841	2872	12620
Males *	252 (30%)	305	-
Females *	589 (70%)	2467	-
Mean age *	44.7 ys	36.4 ys (Migr CAS+) 42.2 ys (Migr CAS−)	48 ys
Migraine CAS+ *	226 (26.9%) (uCAS)	89 (3.1%)	7179 (57%)
Episodic migraine *	-	-	-
E. migraine CAS+ *	-	-	-
E. migraine CAS− *	-	-	-
Chronic migraine *	-	-	-
C. migraine CAS+ *	-	-	-
C. migraine CAS− *	-	-	-
Aura *	-	-	-
Aura CAS+	-	-	-
Aura CAS−	-	-	-
Unilateral migraine *	211	1229	-
U. migraine CAS+ *	87 (38.5%)	56 (62.9%)	-
U. migraine CAS− *	124 (20.1%)	1173 (42.3%)	-
Bilateral migraine *	630	33 (37.1%)	-
Familiarity *	-	42 (47.2%)	-
One CAS *	98 (44%)	-	-
>1 CAS *	128 (56%)	-	-
Lacrimation °	91 (40.3%)	63 (70.8%)	3031 (24%)
Conjunctival injection °	57 (25.2%)	30 (33.7%)	1615 (13%)
Eyelid edema °	36 (15.9%)	-	-
Rhinorrea °	41 (18.1%)	4 (4.5%)	1439 (11%)
Nasal congestion °		n.r.	1362 (11%)
Miosis °	44 (19.5%)	3 (3.4%)	752 (6%)
Ptosis °		6 (6.7%)	1747 (14%)
Forehead sweating °	-	11 (12.4%)	4909 (39%)

"-", not reported; CAS, unilateral Cranial Autonomic Symptoms; "*" percentage value referred to the total of cases; "°" percentage value referred to set Migraine CAS+.

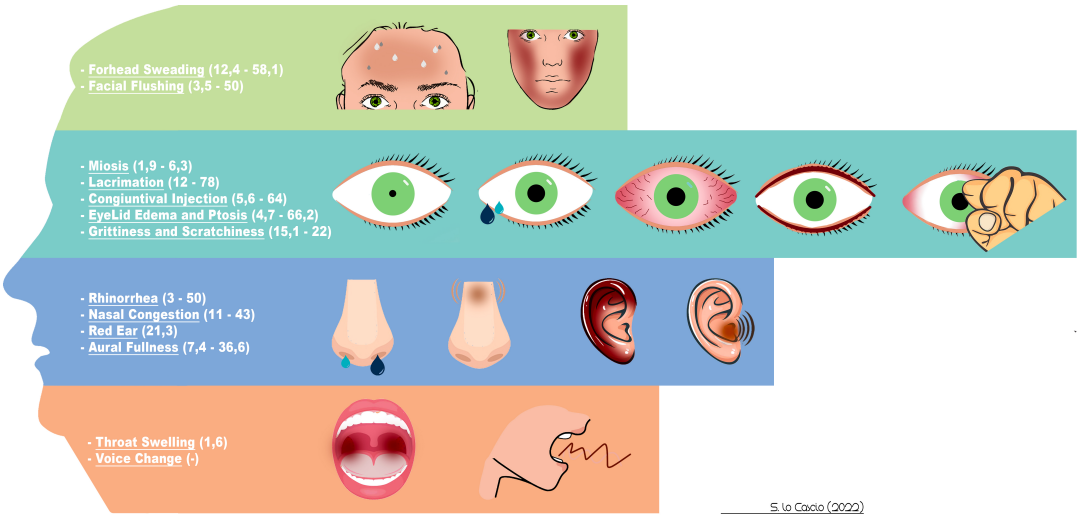

Fig. 1. Autonomic Cranial Symptoms and Prevalence. Schematic and figurative illustration of all autonomic cranial symptoms in migraine and their prevalence (%) based on literature review. Illustration by Salvatore Lo Cascio.

Table 2. Migraine with cranial autonomic symptoms, studies on clinical series in adults.

Authors (ref no.)	P. Barbanti *et al*. 2002 [4]	R. Gupta 2007 [6]	TH Lai *et al*. 2009 [8]	H. Guven *et al*. 2012 [11]	YW Shin *et al*. 2015 [15]	S.Nasir *et al*. 2016 [17]	N. Riesco *et al*. 2016 [18]
Cases	177	78	786	186	769	105	100
Males *	30 (16.9%)	17 (22%)	161 (20.4%)	19 (10%)	142 (18.5%)	43 (40.9%)	7 (7%)
Females *	147 (83.1%)	61 (78%)	625 (79.6%)	167 (90%)	627 (81.5%)	62 (59.1%)	93 (93%)
Mean age *	38 ys	32 ys	40 ys	36 ys	48 ys	35 ys	45 ys
Migraine CAS+ *	96 (54.2%)	57 (73.1%)	437 (56%)	77 (41.4%)	-	74 (70.5%)	82 (82%)
Episodic migraine *	177	48 (61.5%)	481 (62%)	111 (59.7%)	-	-	-
E. migraine CAS+ *	-	-	267 (55.5%)	41 (37%)	-	-	-
E. migraine CAS− *	-	-	214 (44.5%)	70 (63%)	-	-	-
Chronic migraine *	-	11 (14.1%)	305 (38%)	-	-	-	100 (100%)
C. migraine CAS+ *	-	-	174 (57%)	-	-	-	82 (82%)
C. migraine CAS− *	-	-	131 (43%)	-	-	-	-
Aura *	20 (11.2%)	19 (24.4%)	40 (5%)	75 (40.3%)	-	-	-
Aura CAS+	13 (65%)	-	19 (48%)	36 (48%)	-	-	-
Aura CAS−	7 (35%)	-	21 (52%)	39 (52%)	-	-	-
Unilateral migraine *	163 (92%)	37 (47.4%)	487 (61.9%)	129 (69%)	-	-	-
U. migraine CAS+ *	82 (50%)	26 (70.2%)	275 (56.4%)	64 (50%)	-	-	-
U. migraine CAS− *	81 (50%)	11 (29.8%)	212 (43.6%)	65 (50%)	-	-	-
Bilateral migraine CAS+ *	-	31 (40%)	-	3 (1.6%)	-	-	-
Familiarity in CAS+ °	72 (75%)	-	-	41 (53.2%)	-	-	-
One CAS *	22 (23%)	-	227 (51.9%)	27 (35%)	-	50 (47.6%)	28 (34.1%)
>1 CAS *	74 (77%)	-	210 (48.1%)	50 (65%)	-	55 (52%)	54 (65.9%)
Lacrimation °	53 (55%)	34 (59.6%)	193 (44.3%)	42 (54.5%)	93 (12%)	33 (44.4%)	49 (59.7%)
Conjunctival injection °	29 (30%)	28 (49.1%)	104 (23.8%)	40 (51.9%)	119 (15.5%)	23 (31%)	44 (53.6%)
Eyelid edema °	51 (53%)	20 (35%)	68 (15.6%)	51 (66.2%)	89 (11.6%)	17 (23%)	39 (47.6%)
Rhinorrea °	48 (50%)	8 (14%)	110 (25.2%)	-	23 (3%)	22 (29.7%)	20 (20.4%)
Nasal congestion °			94 (21.5%)	20 (25.9)	49 (6.4%)	26 (35.1%)	-
Miosis °	-	-	-	-	-	-	-
Ptosis °	-	-	-	-	100 (13%)	-	42 (51.2%)
Forehead sweating °	-	-	226 (51.7%)	-	99 (13%)	43 (58.1%)	-
Flushing facial °	-	-	-	-	-	-	-
Aural fullness °	-	-	-	-	-	-	30 (36.6%)
Throat swelling °	-	-	-	-	-	-	-
Voice change °	-	-	-	-	-	-	-
Eye grittness °	-	-	-	-	-	-	-

"-", not reported; CAS, unilateral Cranial autonomic Symptoms; "*" percentage value referred to the total of cases; "°" percentage value referred to set Migraine CAS+.

Table 3. Migraine with cranial autonomic symptoms, studies on clinical series in adults.

Authors (ref no.)	P. Barbanti *et al.* 2016 [19]	M. Ceylan *et al.* 2019 [20]	D. Danno *et al.* 2020 [22]	M. Fatima *et al.* 2021 [23]	A. Qavi *et al.* 2021 [24]	M. Tohgha *et al.* 2021 [25]	N. Karsan *et al.* 2022 [26]
Cases	757	1080	373	132	50	904	340
Males *	153 (20.2%)	187 (17.3%)	105 (28.8%)	23 (17.4%)	14 (28%)	206 (22.8)	65 (19%)
Females *	604 (79.8%)	893 (82.7%)	268 (71.2%)	109 (82.6%)	36 (72%)	698 (77.2)	285 (81%)
Mean age *	37–40	31 ys	39 ys	26 ys	27.7 ys	38ys	43 ys
Migraine CAS+ *	283 (37.4%)	749 (69.4%)	158 (42.4%)	73 (55.3%)	36 (72%)	551 (60.9)	251 (74%)
Episode migraine *	535 (70.7%)	897 (83%)	173 (46.3%)	-	50 (100%)	508 (56.1)	75 (22%)
E. migraine CAS+ *	190 (35.5%)	611 (68.2%)	66 (38.1%)	-	-	286 (51.9)	-
E. migraine CAS− *	345 (64.5%)	286 (31.8%)	107 (61.9%)	-	-	222 (48.1)	-
Chronic migraine *	222 (29.3%)	183 (17%)	200 (53.7%)	-	-	396 (43.9)	265 (78%)
C. migraine CAS+ *	93 (41.9%)	138 (75.4%)	92 (46%)	-	-	219 (55.3)	-
C. migraine CAS− *	129 (50.1%)	45 (24.6%)	108 (54%)	-	-	93 (44.7)	-
Aura *	116 (15.3%)	363 (33.6%)	41 (15.3%)	-	6 (12%)	99 (10.9)	183 (54%)
Aura CAS+	39 (13.7%)	-	16 (39%)	-	-	68 (68.6)	-
Aura CAS−	77 (16.2%)	-	25 (61%)	-	-	31 (31.5)	-
Unilateral migraine *	524 (69.2%)	-	182 (48.7%)	97 (73.9%)	38 (76%)	434 (48)	272 (80%)
U. migraine CAS+ *	228 (43.5%)	-	78 (42.8%)	53 (54.6%)	-	285 (65.6)	-
U. migraine CAS− *	296 (56.5%)	-	104 (57.2%)	44 (45.4%)	-	149 (34.4)	-
Bilateral migraine CAS+ *	233 (30.8%)	-	78 (20%)	20 (15.1%)	12 (24%)	217 (24)	-
Familiarity in CAS+ °	-	-	-	-	14 (28%)	-	-
One CAS *	150 (53%)	-	76 (48.1%)	32 (33%)	-	-	-
>1 CAS *	133 (47%)	-	82 (51.9%)	65 (67%)	-	-	-
Lacrimation °	178 (63%)	460 (61.4%)	52 (32.9%)	41 (56.3%)	28 (78%)	151 (27.4)	102 (40%)
Conjunctival injection °	16 (5.6%)	480 (64%)	42 (26.6%)	19 (26%)	12 (33.3%)	164 (29.7)	76 (30%)
Eyelid edema °	135 (47.7%)	441 (58.9%)	12 (7.5%)	10 (13.7%)	23 (64%)	44 (7.9)	52 (20.7%)
Rhinorrea °	108 (38.1%)	93 (12.4%)	37 (23.4%)	21 (28.7%)	-	75 (13.6)	57 (22.7%)
Nasal congestion °		306 (40.8%)	43 (27.2%)	23 (31.5%)	6 (16.7%)	109 (19.8)	108 (43%)
Miosis °	-	-	3 (1.9%)		-	-	-
Ptosis °	-	-	8 (5%)	3 (4.1%)	-	127 (23)	62 (24.7%)
Forehead sweating °	-	279 (37%)	11 (7%)	19 (26%)	-	-	-
Flushing facial °	-	-	9 (6%)	14 (19.2%)	18 (50%)	-	56 (22.5%)
Aural fullness °	-	-	47 (29.7%)	16 (21.9%)	13.1 (36%)	-	85 (33.9%)
Throat swelling °	-	-	-	-	-	-	4 (1.6%)
Voice change °	-	-	-	-	-	-	-
Eye grittness °	-	-	-	-	-	-	38 (15.1%)

"-", not reported; CAS, unilateral Cranial autonomic Symptoms; the study of Karsan *et al.* [26] showed result for two different cohorts of subjects; "*" percentage value referred to the total of cases; "°" percentage value referred to set Migraine CAS+.

In these studies that report the intensity of CAS in the course of a migraine attack, it is usually referred to as milder than that found in individuals with cluster headaches [8,28], however this is a fact that must be confirmed because it may be due to several reasons, see the retrospective nature of the studies.

An interesting study by Viana *et al*. [37] on the variability of the clinical migraine phenotype recording three consecutive attacks, highlighted that, where CAS were present, they tended to occur in all three attacks in a percentage equal to 70% higher than those recorded for classic symptoms such as pain intensity, nausea, quality of pain, one-sidedness, photo-phonophobia, supporting the idea that in CAS+ migraineurs they are part of the specific cluster of migraine attack. The small number of the sample and the limited number of attacks recorded do not allow definitive conclusions. Lai *et al*. [8] showed that consistency of CAS in migrainous attacks was less than that in Cluster Headache. The study also showed that the CAS were milder and more bilateral in migraine subjects compared to the cluster headache. Their data were collected retrospectively.

Another study [27] evidenced that CAS+ migraineurs had significantly a greater central sensitization scored by the validated central sensitization inventory (CSI), suggesting a role of cranial parasympathetic activation to activate the central sensitization. This study support the Yarnitsky *et al*. [38] study that suggested that the role of cranial parasympathetic outflow to sensitize the intracranial nociceptors and to induce parasympathetically indipendent allodynia by sensitizing central trigeminal nociceptors.

Further indications on the correlation between CAS and pathophysiological mechanisms come from two studies that highlight how CAS are more present in migraine sufferers with attacks related to a seasonal cyclicality (also presenting greater disability) [15] and their correlation with cigarette smoking occurring more frequently in smoking migraineurs [9]. These two aspects, cyclicity of attacks and positive history of cigarette smoking, are part of the characteristics reported in subjects with cluster headaches and therefore suggest a link between the two groups and the involvement of similar anatomical-functional structures [9].

The study of Karsan *et al*. [39] suggests that the pain is not necessary to activate the CAS, as also showed for the Cluster Headache, supporting the hypothesis that CAS are not simply due to more severe migrainous attacks with a cascade involvement.

Almost all studies tried to correlate the presence of CAS in migraine attacks with the other clinical features of migraine. Several studies have shown a positive correlation between CAS and chronic migraine [18,25], history of disease [6,11], frequency of attacks [13,21,26], severe intensity of pain [4,17], duration of attacks [6,17], unilaterality of pain [4,11,16,17,25,26], allodynia [17,22], phono/photophobia [6,17] and osmophobia [22]. However the different studies, compared among them, often conflict with each other, not confirming the correlations reported by the other studies and vice versa. The Danish group's [28] study showed a weak correlation between symptoms, no more 0.41, and no clear clustering of symptoms. This is probably due to different selection of samples (prevalence of episodic versus chronic migraine), type of interview, age of the sample, symptom examined, etc. For this reason, although the literature on the subject is now fairly extensive, we agree with the conclusions by the Danish group [28] to study better this possible endophenotypic migraine. They suggest precise diagnostic criteria, differentiated according if they are aimed at genetic and/or epidemiological studies or clinical and/or pathophysiological studies.

Finally the involvement of cranial autonomic activity in migraineurs suggests that in this subgroup of migraineurs general autonomic activity may be more present than those with CAS. Raieli *et al*. [13] reported that pediatric migraineurs with cranial autonomic symptoms had more frequent general autonomic symptoms: vasomotor in 56% and GI dysfunction such as abdominal pain, cramping, early satiety, and persistent fullness in 42%. Recently Togha *et al*. [25] report that visceral symptoms were present about 52% of migraineurs that also reported CAS. However the authors do not precise the correlation between CAS and visceral autonomic symptoms.

2.3 CAS and Migraine Treatment

The presence of a possible endophenotypic subgroup in migraines obviously led to the question if this could have any significance in response to treatment.

Barbanti *et al*. [5] and others [40,41] suggested a greater response to triptans in CAS+ migraine subjects based on large-scale recruitment of peripheral neurovascular 5-HT1B/1D receptors consequent to the activation of the trigeminal autonomic reflex. Further they [10] supported their hypothesis with a double-blind study with Rizatriptan on CAS+ migraine sufferers demonstrating large gains at pain free at 2 hours.

Sarchielli's study [35], made on migraine responders and non-responders to Rizatriptan, is interesting. The authors showed that migraine responders had more CAS than non-responders, as well as having more severe and one-sided pain. In addition, baseline vasoactive intestinal polypeptide (VIP) level was higher and decreased after treatment in CAS responders.

Further confirmation that triptans are more effective in migraine sufferers with CAS+ comes from the study by Viana *et al*. [29] using frovatriptan, resulting their presence as a predictor of response together with unilateral pain, the presence of phonophobia and one or more prodromes.

Curiously, but perhaps not too much, this better response to triptans in CAS+ migraine sufferers was not found in a study conducted in a pediatric population [30]. This data further confirms that the results from the studies in

Table 4. Migraine with cranial autonomic symptoms, studies on clinical series in pediatric age.

Authors (ref no.)	A. Gelfand *et al*. 2013 [12]	V. Raieli *et al*. 2014 [13]	V. Raieli *et al*. 2015 [14]	Z. Haytoglu *et al*. 2019 [22]
Cases	125	202	374 (40 children <7 ys)	170
Males *	50 (40%)	96 (47.5%)	188 (20 children <7 ys).	61 (36%)
Females *	75 (60%)	106 (52.5%)	186 (20 children <7 ys)	109 (64%)
Mean age *	13.1 ys	10.7 ys	5.7 ys (children <7 ys) 11.3 ys (children >7 ys) 192/374 (51.3%)	13.1 ys
Migraine CAS+ *	87 (69.6%)	111 (55%)	22/40 (55%) children <7 ys 170/334 (51%) children >7 ys	68 (40%)
Episodic migraine *	67 (53.6%)	202 (100%)	374 (100%)	97 (57%)
E. migraine CAS+ *	-	-	192 (51.3%)	-
E. migraine CAS− *	-	-	-	-
Chronic migraine *	58 (46.4%)	-	-	73 (43%)
C. migraine CAS+ *	-	-	-	-
C. migraine CAS− *	-	-	-	-
Aura *	32 (25.6%)	27 (13.4%)	48/374 (12.8%)	55 (32.3%)
Aura CAS+	-	19/111 (17.11%)	-	-
Aura CAS−	-	8 /91 (8.8%)	-	-
Unilateral migraine *	20 (16%)	57 (28%)	121 (32.3%) 9/40 (22.5%) children <7 ys 112/334 (33%) children >7 ys	51 (30%)
U. migraine CAS+ *	-	17 (29.8%)	-	-
U. migraine CAS− *	-	40 (70.2%)	-	-
Bilateral migraine *	65 (52%)	135 (67%)	253 (67.7%)	119 (70%)
Familiarity *	-	184 (91%)	-	109 (64%)
One CAS *	38/87 (43.7%)	34 /111 (30.6%)	-	31/68 (45.6)
>1 CAS *	49/87 (56.3%)	77/111 (69.4%)	-	37/68 (54.4)
Lacrimation °	30 (24%)	34 (18.3%)	-	40 (23.5%)
Conjunct.inject °	27 (21.6%)	37 (16.4%)	-	28 (16.4%)
Eyelid edema °	10 (8%)	16 (7.9%)	-	8 (4.7%)
Rhinorrea °	11 (8.8%)	17 (8.4%)	-	14 (8.2%)
Nasal congestion °	19 (15.2%)	29 (14.4%)	-	-
Miosis °	-	7 (6.3%)	-	-
Ptosis °	22 (17.6%)	22 (10.9%)	-	-
Facial sweating °	30 (24%)	26 (12.9%)	-	-
Flushing facial °	-	42 (20.8%)	-	6 (3.5%)
Gritness in eye °	22 (17,6%)	-	-	-
Red ear °	-	43 (21.3%)	-	-
Aural fullness °	35 (28%)	-	-	12 (7.4%)

"-", not reported; CAS, unilateral Cranial Autonomic Symptoms; "*" percentage value referred to the total of cases; "°" percentage value referred to set Migraine CAS+.

adults cannot be adapted tout court in the pediatric population.

Considering the proportion of subjects with chronic migraine CAS+, some authors [32–34] suggest to evaluate the better efficacy of Onanbotulinum toxin treatment on this population into account that some studies suggest different responses to this treatment based on the different clinical phenotype such as quality and direction of pain migraine [42].

Anedoctical case report showed a good efficacy of oxygen in a patient with severe migrainous attacks with CAS, further linking migraine and cluster headache [31].

Finally to our opinion it will be important to evaluate the efficacy of Antibodies anti-calcitonin gene-related peptide (CGRP) in this subgroup of migraineurs, however remembering the importance of VIP levels in this population, while a study showed no difference between CGRP levels in migraineurs CAS+ and CAS– [43].

2.4 CAS and Migraine Prognosis

The prevalence of CAS in subjects with chronic migraine versus those with episodic migraine [8,19–22] suggested that the increased frequency of attacks may induce sensitization and greater involvement of the autonomic component due to the greater severity of disease. How-

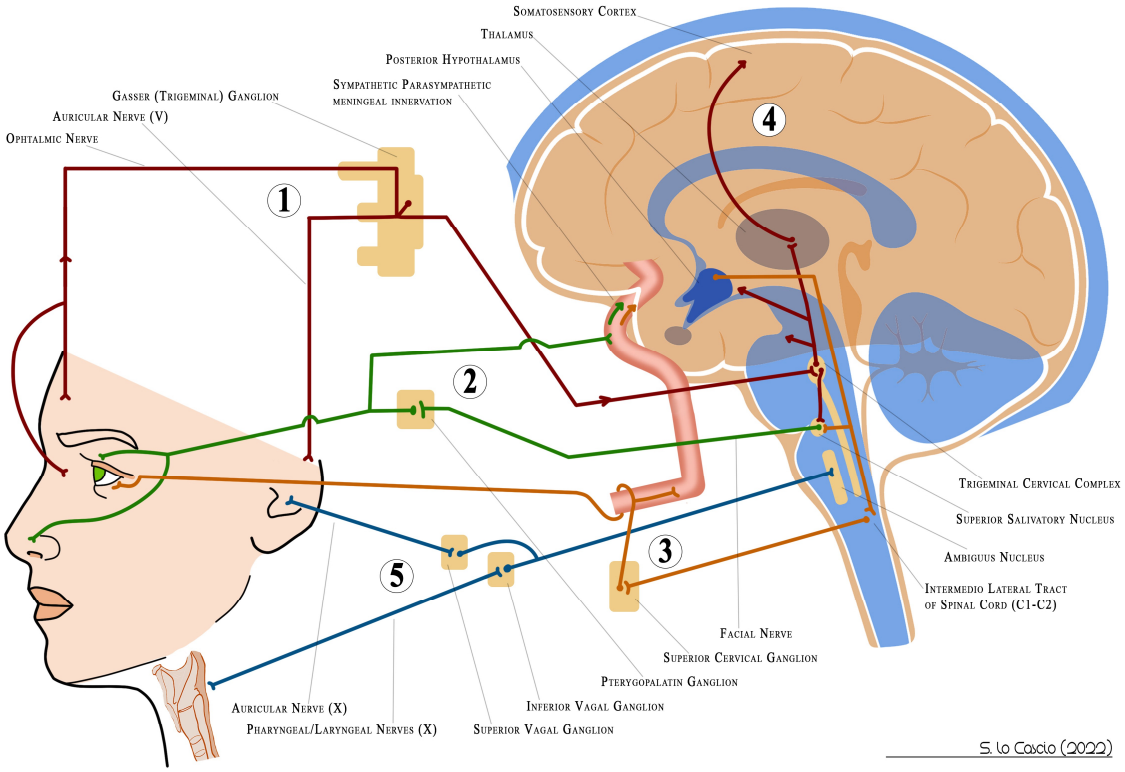

Fig. 2. Pathophisiologic pathway of Migraine and Autonomic Cranial Symphtomps correlated. ① Trigeminal Reflex. ② Cranial parasympathetic activation mediated by Facial Nerve. ③ Sympathetic modulation. ④ SNC activation, thalamus and somatosensory cortex to pain, posterior hypothalamus to autonomic modulation. ⑤ Possibile anatomic patway for aural fullness, throat swelling and voice change. Illustration by Salvatore Lo Cascio.

ever, the evidences (1) that CAS, can also be induced in the absence of pain [39], (2) that this difference between episodic and chronic migraines is not always present in the studies, and (3) that they are already present in pediatric age and with no significant differences between preschool and school age children [12–14], also suggest the alternative hypothesis that CAS are an independent endophenotypic migraine subgroup. The absence of short- and long-term prospective follow-up studies on large samples do not allow for precise conclusions. However, we report an our long-term follow-up study [44] conducted on a small sample of migraine children under 6 years suggesting that CAS may be a predictor of the persistence and worsening of migraine syndrome over time and suggest early treatment as pharmacological as no-pharmacological strategies.

3. Anatomy and Physiopatology

Headache pain is commonly associated with the presence of autonomic symptoms [45], which are the result of the activation of different electro-neurological pathways (Fig. 2). The trigeminal system is an intricate cranial nerve network originating from the 5th pair of cranial nerves. It originates from the pons (structure in the center of the brain), at the upper edge with a small motor root (masticatory nucleus) and a large sensory root (caudate nucleus).

The sensitive part is constituted by the great Gasser ganglion which contains the T neurons from which two pathways branch off, a central one towards the trigemino -cervical complex (TCC) and a peripheral one divided into three branches (ophthalmic, maxillary, mandibular), which receives the sensitive signal coming from all the peripheral territories innervated [46].

In addition to peripheral extracranial innervation, there is a peripheral intra-cranial trigeminal innervation that affects the leptomeninges exclusively trought nociceptive somato-sensory receptors [44], confirmed by presence of small myelinated A-delta fibers (1–6 μm) and Unmyelinated C (0.1–0.4 μm), classically related to nociceptors. To this we must add the innervation of the cerebral vessels mediated by the autonomic system and still little known due to the complex relationship between nociceptive sensitivity and neurogenic control of cerebral circulation [45–47].

Schematically, the cerebral blood vessels are innervated by the trigeminal, sympathetic and parasympathetic sensory nerves with the exact function of each still today debated [45], but all three are important for cerebral blood flow control and perception of pain.

The sympathetic innervation derived from the superior cervical sympathetic ganglion, from the sympathetic ganglia and the middle cervical stellate ganglia [46] and have

a vaso-constricting effect. Parasympathetic innervation, which promotes vasodilation, originates from the sphenopalatine and otic ganglia.

So at the centre of the pathophysiology of neurovascular headaches is the trigemino-vascular system; activation of the trigeminal nerve can explain the pain and may initiate some of the autonomic manifestations. With this system, other structures work in physiopathological synergy: the parasympathetic system and hypothalamus (especially the paraventricular and lateral nuclei whose descending projections reach the TCC and the superior salivatory nucleus (SSP), activating somatosensitive and autonomic neurovascular mechanisms) [46]. Thus, from the trigeminal nuclear complex of the brainstem, somatosensitive information is propagated to the hypothalamus, thalamus, basal nuclei, locus coeruleus and peri-acqueductal grey matter, with propagation of the nociceptive signal to various brain areas [45,46]. Some mediators are involved in this process, such as: calcitonin-gene-related (CGRP), nitric oxide (NO) and vasoactive intestinal peptide (VIP) [47,48].

Other correlations concern the possible involvement of the suprachiasmatic nucleus, situated in the anterior part of the hypothalamus dorsal and above the optic chiasma, which is correlated with the dorsal medullary reticular substance and through sympathetic projections to the parasympathetic pterygopalatine ganglion and the trigeminal sensory nuclei [49]; after all now the hyphothalamus role in the generation of headache attacks is demonstrated by known relevance to the trigeminal reflex and increased connection with the limbic area [50,51].

The spheno-palatine-ganglion (GSP) plays a specific role in headache disorders as a key peripheral structure responsible for the expression of cranial autonomic symptoms, most commonly seen in trigeminal autonomic cephalalgia (TAC) [52]. It receives multiple pathways: parasympathetic pathways coming directly from the superior salivatory nucleus via the facial nerve and sympathetic pathways coming from the superior cervical ganglion via the deep petrous nerve. From it originate: naso-palatine nerve, greater palatine nerve, lesser palatine nerve, posterior, superior and inferior lateral nasal branches and pharyngeal branch of maxillary nerve [52]. These branches project to the vessels of the skull, nasal and oral mucosa, and lacrimal glands, and the activity of the parasympathetic innervation increases naso-palatal secretion, and the activity of the sympathetic is inhibitory to the same function [52].

Trigeminal afferents stimulate the SSN, going on to activate parasympathetic postganglionic neurons in the GSP. stimulation of the GSP, as shown by various studies, activates cerebral vasodilation and increases cerebral blood flow [47]. Activation of GSP may result in the release of acetylcholine, vasoactive intestinal peptide (VIP) and nitric oxide in dural blood vessels, the result could be the overflow of plasma proteins resulting in neurogenic inflammation and activation of trigeminal nociceptors that contribute to pain and trigger headaches. Finally, dysfunction of sympathetic output results in ptosis and miosis [38,47–49,51–54].

4. Open Questions

The scientific literature has clearly established that CAS are present in a large group of migraine sufferers, both in general and clinical population studies. Furthermore, the data suggest their presence more in chronic migraine than in episodic migraine (see Tables 2,3), however it remains an open question that this prevalence is due to the duration of the disease and frequency of attacks because this assumption is not justified by the presence of them in a fair amount of children, even under the age of seven [13,14], where obviously the duration of disease is very short and also the frequency of attacks. Probably, sensitization mechanisms facilitate their appearance but there aren't "ad hoc" studies including neurophysiological factors, but it's possible that genetic factors coexist selecting this subgroup since the developmental age. From a clinical point of view, an open question concerns the variability of these symptoms in different populations, so it is not clear which ones to include in this list, which ones are most representative, if there is a tendency to segregate each other in a specific way, if the prevalence of one specific with respect to another implies a different clinical meaning, if there is a specific correlation with other symptoms of the migraine phenotype. Studies on large cases with a precise phenotypic characterization and with adequate follow-up could clarify these important clinical aspects.

Studies generally tend to suggest that migraineurs with CAS have more severe attacks, more frequent and perhaps longer [4,6] but we do not know if it is the severity of the migraine manifestation that determines parasympathetic activation or vice versa parasympathetic activation plays a causal role in determining the severity of the migraine attack. Studies showing that CAS+ migraine sufferers have a better response to triptan therapy (both rizatriptan and frovatriptan) [5,10,29,35] suggest, in our opinion, the second hypothesis, also supported by the data from Viana *et al*. [29] where in the phenotypic variability of migraineurs during three attacks CAS were among the features that most tended to occur in all three attacks, significantly more than symptoms as quality of pain, severity of pain, nausea, phono/photo phobia, suggesting that CAS, where present, may be persistent traits of the migraine phenotype in this subgroup of migraineurs. If they are identified as clinical markers since childhood and as predictive factors of the evolution of the disease and of the response to therapies, they can give early and precise indications on which treatments to adopt.

Another question that is open as well as important, is to clarify the predictivity of the response to drugs in the presence of CAS. Preliminary data suggest that triptans respond better in the presence of CAS [5,10,29,35] and this

has been also suggested for botulinum toxin treatment [32–34]. It should be interesting to address this hypothesis, also for historical and emerging prophylaxis therapies. The results of the anti CGRP monoclonal antibodies (therapy that has modified the migraine treament) are expected in this subgroup, even if the data of a lack of correlation between CGRP and CAS levels [43] could suggest an inverse correlation of response, contrary to triptans and botulinum toxin.

The study made by Johnson *et al*. [30] shows that CAS are not predictive of the response to triptans in pediatric migraine, other proof that the results in adults cannot be automatically adapted in developmental age, and that there is a need for ad hoc studies. The CAS in pediatric age, even in the presence of few studies, are convincing for their presence in migrainous children, even earlier, and could be predictive on the evolution of the disease in the long-term follow-up. However, it is not clear whether they are determined by genetic factors, also inherited from parents, or by early exposures that can determine autonomic hyperexcitability [44] and are necessary studies on large populations well described and followed prospectively over time, possibly associated with neurophysiological and functional neuroimaging studies.

Concluding, open questions are different and of considerable importance, not only pathophysiological, but most importantly for the caretaking of our patients. Furthermore these data reopen a fundamental discussion about the relationships between primary headache disorders (see modular theory [55]) also because the TACs have been differentiated from migraines and grouped together precisely because of the presence of the CAS.

Final Considerations

According to the 3rd IHS classification [2], migraine can be diagnosed on these main clinical aspects that underlie specific pathophysiological mechanisms: (1) temporal recurrence of the attacks; (2) duration of the painful attack (not less than 2 hours including the pediatric age); (3) the characteristics of pain in terms of unilateral lateralization, pulsating quality, pain severity and increasing with routine physical activity; (4) involvement of the general vegetative system (nausea and/or vomiting) and intolerance of sensory channels (photophobia and phonophobia). The migrainous patient, due to the current absence of specific biomarkers, is identified on the basis of the association of these clinical aspects which must not necessarily be present all in the single patient. The subject identified as migrainous will be included in the pharmacological and functional studies, however it is evident that, already on the basis of these diagnostic criteria, migrainous subjects with different clinical characteristics (for example duration of the attack, quality of pain, bilateral pain, vomiting present or absent etc) can be included in the studies, being able to arise conflicting results.

Indeed, migraine is a very complex disorder that involves multiple structures of the nervous system and has a complex clinical heterogeneity not sufficiently highlighted by the current diagnostic criteria. Over the years, the presence or absence of clinical features such as allodynia, osmophobia, general prodromes and autonomic symptoms can affect the therapeutic response and clinical outcome of the individual migraine sufferer.

In this general premise the attention placed, about 20 years ago, on the presence of CAS in migraine attacks (well described anecdotally in migraine patients) must still be placed. They are interpreted as a clinical expression of the hypothesized trigemino-autonomic reflex and they are the basis of the distinction of TACs, as an autonomous group of primary headaches of the IHS Classification. Their presence in a conspicuous proportion of migraine sufferers, both pediatric and adult, raises questions for the physiopathological aspects of migraine, on the relationship with TACs on the evidence of different behaviors in the therapeutic response and in abortive therapies of the migraine attack and on the evolution over time of the migraine syndrome in the individual patient. As for allodynia, they must be also identified and accurately described in the phenotypic characterization of the migraine attack in our patient, suggesting a more adequate intervention.

They, together with other clinical features of the migraine attack, such as allodynia, osmophobia, migraine aura, the quality of pain, general symptoms dued to para/orthosympathetic activity, etc., as well as highlighting the multifaceted and rich expression of the migraine attack in different subjects, invite the doctor to make a more individualized diagnosis of the patient because his response to therapy and to the modification of the clinical course also depends on this.

5. Conclusions

CAS are present in the attacks of a significant proportion of migraineurs and their presence is an expression of the involvement of the autonomic system and probably has a significance for prognosis and treatment of migraine. therefore they must be sought and taken into account during the visit of migrainous patient.

Author Contributions

Conceptualization—VR; Data investigation—SLC, EC, SD, MC, AM, RM, and SLN; Analysis of data—SLC, EC, SD, AM, RM, SLN and VR; Tables—SLC, EC, MC and VR; Iconography—SLC; Supervision—VR; Writing—review and editing—SLC, EC, SD, MC, AM, RM, SLN and VR. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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