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## ΕΙΔΙΚΟ ΤΕΥΧΟΣ / SPECIAL ISSUE
## ΚΕΦΑΛΑΛΓΙΕΣ / HEADACHES



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Ιούλιος - Αύγουστος 2022 / July - August 2022

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## Editorial for the Special Issue "Headaches"

We are pleased to present a Special Issue of the *"Archives of Clinical Neurology"*, a Journal of the Hellenic Neurological Society, on the topic of "Headaches".

Migraine is the most prevalent neurological disorder, causing significant burden to large population groups. During the last decade, extensive research has added a lot to our understanding of migraine pathophysiology, and a number of new treatment options both for preventive and acute use have been approved, with more expected in the next few years. Other headache types, including cluster headache, are less prevalent but even more disabling and excruciating in terms of pain intensity. Novel treatments have also been added to our armamentarium against this headache type, and providing relief to our patients is more feasible than ever in the past.

In this special issue, a collection of review articles with ongoing information focusing on the pathophysiology, clinical manifestations, diagnosis, and treatment approaches of migraine and cluster headache is presented, encompassing all the newest advancements. In addition, an excellent review article on the neuroradiological findings on common or uncommon secondary headaches enriches our knowledge on the always important issue of ruling out secondary causes in order to confirm a primary headache diagnosis.

We firmly believe that this collection offers a useful and up-to-date guide for clinical neurologists.

We would like to thank all authors who have contributed to this special issue.

**Michail Vikelis**
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# Άρθρα...

# ΗΜΙΚΡΑΝΙΑ ΚΑΙ CALCITONIN PEPTIDE FAMILY: ΤΙ ΠΑΡΑΒΛΕΠΟΥΜΕ ΕΣΤΙΑΖΟΝΤΑΣ ΜΟΝΟ ΣΤΟ CGRP ΚΑΙ ΣΤΟΝ ΥΠΟΔΟΧΕΑ ΤΟΥ;

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**Περίληψη**

Τα νέα φάρμακα που κυκλοφόρησαν πρόσφατα και αφορούν στην αντιμετώπιση της ημικρανίας έχουν ως στόχο το νευροπεπτίδιο Calcitonin-Gene Related Peptide (CGRP) ή τον υποδοχέα του. Η ανταπόκριση των ασθενών στις καινούργιες αυτές αγωγές είναι περίπου 60%. Στο άρθρο αυτό γίνεται αναφορά και σε άλλα νευροπεπτίδια της ίδιας όμως «οικογένειας» (Calcitonin peptide family) και των υποδοχέων τους, ο ρόλος των οποίων στον μηχανισμό της ημικρανίας δεν πρέπει να παραβλεφθεί εστιάζοντας μόνο στο CGRP.

**Λέξεις ευρετηρίου:** ημικρανία, CGRP, αμυλίνη, αδρενομεδουλίνη

# MIGRAINE AND CALCITONIN PEPTIDE FAMILY: WHAT DO WE OVERLOOK BY FOCUSING ONLY ON CGRP AND HIS RECEPTOR?

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**Abstract**

The newly released migraine medications target the Calcitonin-Gene Related Peptide (CGRP) or tis receptor. The response of migraineurs to these new treatments is about 60%. This article mentions other neuropeptides of the same Calcitonin peptide family and their receptors, whose role in the mechanism of migraine should not be overlooked by focusing only on CGRP.

**Key words**: migraine, CGRP, amylin, Calcitonin peptide family, adrenomedullin

Από το 2018 έχουν εγκριθεί από τον υπεύθυνο κυβερνητικό οργανισμό των ΗΠΑ Food and Drug Administration (FDA) σύνολο 6 νέα φάρμακα (4 μονοκλωνικά αντισώματα (mAbs) και 2 πιο μικρά μόρια-gepants) για την προφύλαξη ή για τη συμπτωματική αντιμετώπιση της ημικρανίας που έχουν ως στόχο το νευροπεπτίδιο Calcitonin-Gene Related Peptide (CGRP) ή τον υποδοχέα του. Στη συνέχεια το ίδιο αρχίζει να συμβαίνει -σε σχέση με τις εγκρίσεις- και από τον αντίστοιχο ευρωπαϊκό οργανισμό (EMA). Το γεγονός από μόνο του είναι πρωτόγνωρο για μια νευρολογική πάθηση (τόσα φάρμακα ταυτόχρονα) και ειδικά για την πάθηση της ημικρανίας. Τα νέα αυτά φάρμακα, που μαζί με την Αλλαντική τοξίνη τύπου Α (που εγκρίθηκε από το 2010 για την χρόνια ημικρανία), εστιάζουν είτε στην απελευθέρωση του νευροπεπτιδίου CGRP (αλλαντική τοξίνη τύπου Α), είτε στο ίδιο το CGRP (mAbs = fremanezumab, galcanezumab, eptinezumab) είτε στον υποδοχέα του (mAb = erenumab και gepants) έχουν αναμφίβολα αλλάξει την προφύλαξη της ημικρανίας. Ένας σημαντικός αριθμός ημικρανικών ασθενών επωφελούνται και βελτιώνεται η ποιότητα ζωής τους χωρίς να εμφανίζονται ιδιαίτερες και σοβαρές ανεπιθύμητες ενέργειες. Το ποσοστό ανταπόκρισης (50% responders rate) είναι περίπου 60% [1]. Αμέσως όμως προκύπτει το ερώτημα γιατί οι υπόλοιποι ασθενείς ΔΕΝ ανταποκρίνονται. Και γιατί η ανταπόκριση στον ίδιο τον ασθενή που ανταποκρίνεται (responder) δεν είναι της

τάξεως 90 με 100%; Επίσης γιατί υπάρχει διαφορετικό προφίλ ανεπιθύμητων ενεργειών στους λίγους ασθενείς που αυτές εμφανίζονται; Ο σημαντικός ρόλος του CGRP στην ημικρανία είναι γνωστός εδώ και σχεδόν 40 έτη [2]. Θα έπρεπε το μπλοκάρισμα της δράσης του CGRP να επιφέρει σε πολύ μεγαλύτερο ποσοστό των ασθενών σημαντική βελτίωση. Υπάρχουν οπότε ίσως και άλλα νευροπεπτίδια ή νευροδιαβιβαστές που συμμετέχουν στον μηχανισμό της ημικρανίας και το μπλοκάρισμα της δράσης τους είναι και αυτό σημαντικό για να μην εκδηλωθεί μια ημικρανική κρίση; Εν κατακλείδι, είναι η ημικρανία μια πάθηση του CGRP;

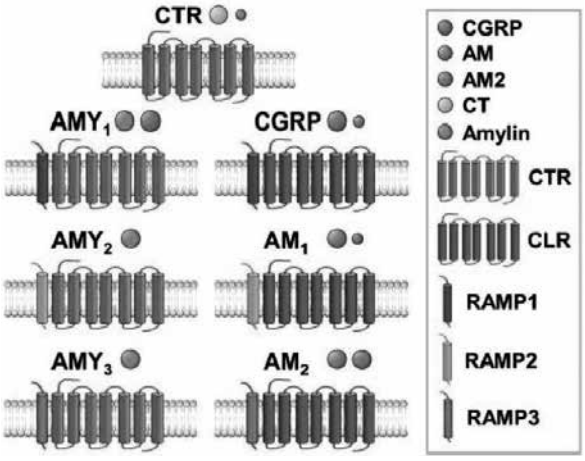
Για τη διερεύνηση αυτών των ερωτημάτων που προκύπτουν, θα πρέπει καταρχάς να γνωρίζουμε ότι το CGRP μαζί με τα πεπτίδια καλσιτονίνη (Calcitonin-CT), την αμυλίνη (amylin), την αδρενομεδουλίνη (adrenomedullin – AM) και την αδρενομεδουλίνη 2 (adrenomedullin 2/ intermedin – AM2/IMD) μπορούν να θεωρηθούν «οικογένεια» – Calcitonin peptide family [3]. Το μήκος των πεπτιδίων της οικογένειας κυμαίνεται από 32 αμινοξέα (CT) μέχρι 52/53 αμινοξέα (AM, AM2/IMD). Το εύρος της βιολογικής δράσης αυτών των πεπτιδίων είναι μεγάλο [3]. Η CT, που έχει ανακαλυφθεί πρώτη, είναι ορμόνη που παράγεται από τα C- Κύτταρα του θυρεοειδούς και ο ρόλος της είναι να μειώνει το ασβέστιο του πλάσματος και να συμβάλλει στη διαμόρφωση των οστών [4]. Το CGRP υπάρχει στα περισσότερα ζωικά είδη σε δυο ισομορφές, α-CGRP και β-CGRP που διαφέρουν σε τρία μόνο αμινοξέα, ενώ σε κάποια ζωικά είδη δεν υπάρχει β-CGRP, αλλά κάποιο άλλο πεπτίδιο αντ' αυτού. Απελευθερώνεται από τις περιαγγειακές νευρικές απολήξεις μετά από ενεργοποίηση του τριδύμου νεύρου και έχει σημαντικό ρόλο στη διαδικασία της ημικρανίας [5]. Ο ρόλος του στη ρύθμιση του καρδιαγγειακού συστήματος, παρά την έντονη αγγειοδιασταλτική του δράση, είναι σημαντικός μόνο σε παθολογικές καταστάσεις μάλλον. Έτσι, το μπλοκάρισμα του CGRP σε υγιείς εθελοντές δεν επιδρά στην αρτηριακή τους πίεση [6]. Τα επίπεδα του στο πλάσμα γενικά είναι πιο υψηλά στις γυναίκες [7]. Η αμυλίνη ανακαλύφθηκε το 1987 όταν απομονώθηκε από εναποθέσεις αμυλοειδούς, που πάρθηκαν μετά θάνατον, από πάγκρεας ασθενών με διαβήτη τύπου ΙΙ [8]. Είναι μια πεπτιδική ορμόνη αποτελούμενη από 37 αμινοξέα, που βρίσκεται μαζί με την ινσουλίνη στα εκκριτικά κοκκία των β-κυττάρων του παγκρέατος [9, 10]. Η αδρενομεδουλίνη απομονώθηκε το 1993 αρχικά από εκχύλισμα ιστού φαιοχρωμοκυττώματος [11], αλλά παράγεται τελικά και από τους πνεύμονες, τους νεφρούς, τον εγκέφαλο, τον στόμαχο, τον πρόσθιο λοβό της υπόφυσης, από την καρδιά, τα λεία μυϊκά κύτταρα των αγγείων και από το ενδοθήλιο των αγγείων που είναι και η κυριότερη πηγή της κυκλοφορούσας αδρενομεδουλίνης [12]. Η δράση του πεπτιδίου αδρενομεδουλίνη 2 δεν είναι ακόμη καλά κατανοητή. Γνωρίζουμε όμως ότι στο ΚΝΣ προκαλεί αύξηση της απελευθέρωσης προλακτίνης, μειώνει την πρόσληψη τροφής και ενεργοποιεί το συμπαθητικό νευρικό σύστημα [13]. Το CGRP και η αδρενομεδουλίνη δρουν ισχυρά αγγειοδιασταλτικά και μάλιστα το CGRP ίσως είναι η πιο αγγειοδιασταλτική ουσία στην φύση που γνωρίζουμε [14, 15]. Η αδρενομεδουλίνη προκαλεί αγγειοδιαστολή αυξάνοντας το ενδοκυττάριο cAMP στα λεία μυϊκά κύτταρα των αγγείων μέσω ειδικών υποδοχέων και σε αυτό συμμετέχει και ο εξαρτώμενος από το ενδοθήλιο αγγειοδιασταλτικός μηχανισμός αυξημένης παραγωγής του νιτρικού οξειδίου [16]. Η αγγειοτενσίνη ΙΙ ανταγωνίζεται τη δράση της αδρενομεδουλίνης [17].

## Υποδοχείς

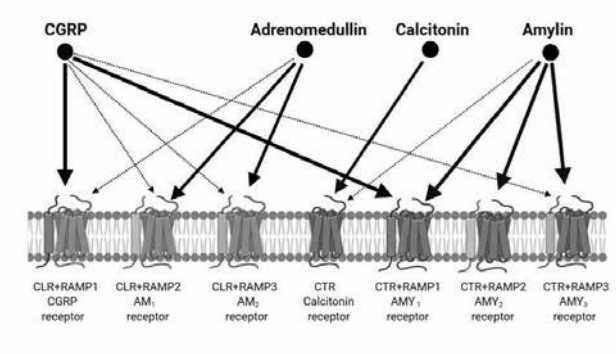
Όλα τα πεπτίδια της οικογενείας δρουν σε υποδοχείς G protein-coupled receptors (GPCRs), και συγκεκριμένα στους class B GPCRs (secretin-like) σύμφωνα με την κατάταξη του 2006 [18] που βρίσκονται στην κυτταρική μεμβράνη και η ενεργοποίηση τους έχει ως αποτέλεσμα την κυτταρική ανταπόκριση. Υπάρχουν δυο τέτοιοι υποδοχείς: ο CT υποδοχέας (CTR) και ο CT receptor-like υποδοχέας (CLR). Επίσης δημιουργούνται επιπλέον υποδοχείς όταν ο CTR και ο CLR υποδοχέας συνδυάζονται με receptor activity-modifying proteins (RAMPs) [19], οι οποίες είναι πρωτεΐνες που τροποποιούν τη δράση των GPCRs υποδοχέων [20]. Υπάρχουν στο σύνολο τρεις RAMPs: RAMP1, RAMP2, RAMP3. Με τους ανάλογους συνδυασμούς, δημιουργούνται στο σύνολο 7 υποδοχείς στους οποίους δρουν τα πεπτίδια της οικογένειας Calcitonin Peptide family και φαίνονται στην Εικόνα 1.

Επίσης στην Εικόνα 2 φαίνεται και η δράση του κάθε πεπτιδίου στον εκάστοτε υποδοχέα. Παραδείγματος χάριν, το CGRP δρα το ίδιο έντονα τόσο στον υποδοχέα CGRP όσο και στον υποδοχέα AMY1 και μάλιστα με την ίδια ένταση που δρα και η αμυλίνη. Η αμυλίνη δρα με την ίδια ένταση και στους τρεις υπο-

**Εικόνα 1.** Οι 7 υποδοχείς των πεπτιδίων της Calcitonin peptides family



**Εικόνα 2.** Η δράση των πεπτιδίων της Calcitonin Peptide Family στους υποδοχείς




δοχείς AMY. Ο CLR υποδοχέας από μόνος του (χωρίς να συνδυαστεί δηλαδή με κάποια πρωτεΐνη RAMP) δεν φτάνει στην επιφάνεια της κυτταρικής μεμβράνης, ενώ ο υποδοχέας CTR χωρίς να συνδυαστεί με RAMP ενεργοποιείται από την CT, ενώ όταν συνδυάζεται με RAMP από την αμυλίνη [3]. Ο υποδοχέας CGRP (CLR-RAMP1), για τον οποίο γίνεται τόσος λόγος τα τελευταία έτη και τον οποίο μπλοκάρει η ερενουμάμπη, αποτελείται από τον συνδυασμό CLR υποδοχέα και RAMP1 πρωτεΐνης και εκτός από το CGRP ενεργοποιείται, σε μικρότερο βαθμό από την αδρενομεδουλίνη.

Οπότε τίθεται το ερώτημα αν συμμετέχει ο AMY1 υποδοχέας στη διαδικασία της ημικρανίας και αν ναι, μπορεί, αν εκλείψει το CGRP, να ενεργοποιήσει τον υποδοχέα η αμυλίνη; Σε μικρότερο βαθμό ισχύει το ίδιο και για τους υποδοχείς AM1 και AM2; Σε μια μελέτη του 2021 μια ουσία ανάλογη της αμυλίνης (pramlintide), δοκιμάστηκε σε 36 ασθενείς με ημικρανία χωρίς αύρα και προκάλεσε στους 30 κεφαλαλγία και 14 από αυτούς είχαν κεφαλαλγία με χαρακτηριστικά ημικρανίας. Οι αντίστοιχοι αριθμοί μετά από χορήγηση CGRP σε αυτούς τους ασθενείς ήταν 33 και 19 και η διαφορά δεν ήταν στατιστικά σημαντική [21]. Κλινικά η ημικρανία από την pramlintide είχε τα ίδια χαρακτηριστικά πόνου και εντόπισης σε σχέση με την ημικρανία που προκαλούνταν από το CGRP. Παρομοίως, η ίδια ομάδα ερεύνησε την ενδοφλέβια χορήγηση της αδρενομεδουλίνης σε 20 ασθενείς με ημικρανία χωρίς αύρα και προκάλεσε στο 55% από αυτούς κρίση ημικρανίας (σε σχέση με 15% της ομάδας ελέγχου που έλαβε εικονικό φάρμακο), ενώ συνολικά το 80% εμφάνισε κεφαλαλγία. Η ένταση του πόνου και η διάρκεια σε αυτούς που έκαναν ημικρανική κρίση ήταν μεγαλύτερα σε σχέση με την ομάδα ελέγχου. Ο πόνος εντοπίζονταν σε μεγάλη αναλογία ινιακά [22].

### Πέρα από το CGRP και τον υποδοχέα του

Τα ερωτήματα που προκύπτουν μετά από την ανακάλυψη της πιθανής επίδρασης και άλλων πεπτιδιών από την calcitonin peptide family στον μηχανισμό της ημικρανίας (αλλά και πιθανοί μελλοντικοί θεραπευτικοί στόχοι) είναι:

Μπορεί το μπλοκάρισμα του AMY1 υποδοχέα ή/και της αμυλίνης να συμβάλουν στην προφύλαξης της ημικρανίας; Και αν ναι, θα πρέπει να γίνεται ταυτόχρονα με το μπλοκάρισμα του CGRP και του υποδοχέα του π.χ. με πολυκλωνικά ή διειδικά μονοκλωνικά αντισώματα; Οι μελέτες σχετικά με την αμυλίνη και τον υποδοχέα της είναι δύσκολες, γιατί μπορεί η αμυλίνη να ενεργοποιεί τόσο τους CTR υποδοχείς που συνδυάζονται με RAMP όσο και τους CTR υποδοχείς που δεν συνδυάζονται (free CTR) [3].

Το ίδιο ερώτημα ισχύει και για την αδρενομεδουλίνη και τους υποδοχείς AM1 και AM2.

Θα πρέπει να διευκρινιστεί ο ρόλος του β-CGRP στην ημικρανία. Το β- CGRP δεν βρίσκεται μόνο στο ΓΕΣ, όπως συχνά διατυπώνεται, αλλά είναι η κυρίαρχη μορφή του CGRP που εκφράζεται στο ΓΕΣ. Έχει όμως και δράση στο ΚΝΣ, μαζί με το α-CGRP στο πρόσθιο κέρας του ΝΜ, ενώ το α-CGRP μόνο του δρα στο οπίσθιο κέρας και στην νευρομυϊκή σύναψη [23]. Δεν θα πρέπει να αποκλειστεί η συμμετοχή του β-CGRP στο μονοπάτι του πόνου της ημικρανίας.

Τέλος, εκτός από την Calcitonin peptide family υπάρχει το ενδεχόμενο και μια άλλη ομάδα πεπτιδίων που ανήκουν στην vasoactive intestinal polypeptide (VIP)/glucagon/secretin family και αποτελούνται από το νευροπεπτίδιο Pituitary adenylate-cyclase-activating polypeptide (PACAP) είτε με την μορφή των 27 αμινοξέων (PACAP-27) είτε με την μορφή των 38 αμινοξέων (PACAP-38) να συμμετέχουν σε όλη τη διαδικασία της ημικρανίας. Προς το παρόν η έρευνα σε σχέση με αυτή την οικογένεια νευροπεπτιδίων δεν έχει δώσει τα αναμενόμενα αποτελέσματα, αλλά συνεχίζεται και πιθανό τα επόμενα χρόνια θα γνωρίσουμε καλύτερα τη δράση αυτών των πεπτιδίων και των υποδοχέων τους που διαφέρουν εντελώς από το μονοπάτι του CGRP.

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# MIGRAINE AND CEREBROVASCULAR DISEASES: AN OVERVIEW

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**Abstract**

Migraine and cerebrovascular diseases are among the most common neurological disorders. While migraine has traditionally been considered a benign condition, increasing evidence points to a strong association with stroke. The latter is strongest for migraine with aura, while migraine without aura doesn't increase the risk of stroke. Women, younger patients, patients with frequent attacks and new-onset migraineurs are mostly at risk of stroke. Smoking and oral contraceptive use further increase the risk. Migraine and cerebrovascular diseases are linked in four ways as migraine can: 1) be a symptom of stroke, 2) be the cause of stroke (i.e. migrainous infarction), 3) increase the risk of stroke and 4) can be a symptom of genetic syndromes predisposing to stroke. Cerebrovascular disease mimicking a migraine attack, while uncommon, can lead to important diagnostic and therapeutic dilemmas. Migrainous infarctions are rare and can only be diagnosed after extensive work-up but must be considered in young stroke patients. Multiple mechanisms have been proposed to explain the association between cerebrovascular disease and migraine, with cortical spreading depression, vascular reactivity and endothelial dysfunction being the most prevalent. The role of patent foramen ovale and microemboli is currently investigated. Unveiling the pathophysiology of migraine-related stroke can help prevent cerebrovascular disease, while recognizing the potential risk factors can help minimize stroke risk in migraineurs.

**Key words**: migraine, stroke, cerebrovascular diseases

## Introduction

Migraine is the most common neurological disorder affecting almost 15% of the population in Europe [1]. In 30% of cases it is associated with transient neurological symptoms (aura) commonly manifesting as visual, sensory and language disturbances and rarely as brainstem-associated or motor deficits [2]. Traditionally, the pathophysiology of migraine has been associated with vascular changes in the brain, the so-called vascular theory. While the latter is not currently considered viable, the association of migraine with cerebral vascular disorders is undisputable.

Migraine is commonly thought of as a benign condition but is linked to cerebrovascular disease in four different ways: 1) headache at the onset, during or after acute cerebrovascular accidents can mimic migrainous headache; 2) migraine may be the cause of ischemic stroke (migrainous infarction); 3) migraine can be a risk factor for cerebrovascular disease (migraine-related strokes) and 4) migraine is a core symptom in genetic syndromes characterized by cerebral ischemia, such as CADASIL and MELAS.

## Migrainous headache due to vascular disease (migraine-mimic)

Headache can in some cases accompany acute cerebrovascular diseases. In subarachnoid hemorrhage (SAH), headache occurs in the majority of patients, with almost all patients presenting with headache at the onset [3]. Cephalalgia preceding hemorrhage is also often reported by patients suffering from aneurysmal SAH and probably represents small sentinel bleeds or changes within the aneurysmal wall [4]. In intracranial hemorrhage (ICH) headache is also common, with most patients reporting headache in the hours following the onset of neurological symptoms. Irritation of pain sensitive intracranial structures by the expanding hematoma or increased intracranial pressure is probably responsible for the headache [3].

In ischemic stroke, headache is less often, probably underestimated and overshadowed by other symptoms. The frequency of headache depends on the study population and design and varies widely between different studies. In TIA or minor stroke headache has been reported in 16-65% of patients, whereas in complete or severe strokes 9-31% of patients report headache. Headache can accompany

the onset of ischemia, so-called onset headache, can precede (sentinel headache) or follow the ischemic event (late-onset headache) [5]. Sentinel headache, while common in impending SAH due to aneurysmal rupture, is present in only 10% of patients with stroke. Onset headache is present in 16-36% of patient with TIA and 8-34% of patients with stroke, while late-onset headache is less strictly defined and less common [3, 6].

Many theories have been proposed to explain headache in acute cerebral ischemia [7]. Dilation of collateral vessels during ischemia and stimulation of the trigeminovascular system, platelet aggregation and degranulation, distention of the vessels proximal to the site of occlusion and toxic effect of the thrombus and the vasoactive agents released are all attractive theories. However, none of these theories can completely explain the headache that accompanies cerebral ischemia. In a study where 38% of patients with acute stroke reported headache, intracranial and extracranial atherosclerosis were inversely associated with headache frequency [8] suggesting that healthy vessel walls are associated with more stroke-associated pain.

Stroke subtype and localization are associated with different prevalence of onset headache. Onset-headache is most common in patients suffering infarcts in the right anterior insular region, the somatosensory cortex of both hemispheres and the cerebellum [9]. Ischemic events in the posterior circulation, traditionally associated with headache, don't seem to have a higher frequency in recent studies [6]. The association of stroke subtype with onset headache is less defined [10]. Headache is less common in lacunar infarcts and cortical involvement is associated with a higher frequency of onset-headache during stroke [6]. Onset-headache frequency in cardioembolic strokes is probably comparable to strokes attributable to large vessel disease. As a consequence, the presence of headache cannot be used for the differential diagnosis between stroke subtypes.

**Migrainous stroke**

Migrainous stroke is considered a complication of migraine with aura. It is defined by ICHD-3 (International Classification of Headache Disorders, 3rd edition) as a migraine attack in a patient with migraine with aura, typical of previous attacks, persisting more than 60 minutes and presenting with typical neuroimaging abnormalities of ischemia in a relevant area. All other diagnoses must be excluded [2]. This definition does not allow the diagnosis of migrainous stroke in individuals suffering from migraine without aura, a point of controversy in several reports. Most studies show that migraine without aura does not increase the rate of stroke, while others disagree. In most cases of migrainous infarction the prognosis is favorable with good recovery [15].

Migrainous infarction is an uncommon diagnosis. It is mostly diagnosed in young women with cryptogenic stroke. Its incidence is estimated at 3,36/100.000/year accounting for 0.2%-0.8% of all ischemic strokes [11, 12]. Most cases present with ischemia located in the posterior circulation [13-15]. In the study by Kruit et al, 65% of migrainous infarction sufferers had lesions in the posterior circulation, with 85% of those located in the cerebellum. Most patients showed multiple round or ovoid lesions in multiple arterial or border zone territories [13].

The underlying mechanism of migrainous infarction is poorly understood. A multitude of theories have been proposed, mainly implicating a reversible decrease in cerebral blood flow that reaches critical ''ischemic'' levels during the aura. This theory is supported by the fact that aura symptoms frequently affect the visual system, which is supplied by the posterior circulation, where most lesions are located in migraineurs [13, 14]. Probable mechanisms include cortical spreading depression (CSD), increased vascular reactivity or endothelial changes.

CSD, the electrophysiological phenomenon that underlies migraine aura, could cause cerebral ischemia. During CSD a depolarizing wave travels the cortex at a rate of 3-5mm/min [16]. This depolarization causes metalloproteinase activation, blood-brain barrier disruption and changes in water and ion homeostasis [17]. This further leads to increased metabolic demands, coupled with raised cerebral blood flow at the onset and followed by cerebral oligemia due to decreased cerebral vascular responsiveness, as shown in a rat model [18]. Thus, CSD can lead to cerebral hypoperfusion and ischemic lesion formation or propagation [19]. Besides CSD, endothelial changes and vasoconstriction are also considered plausible mechanisms of stroke during migraine aura, but most studies show conflicting evidence. Endothelial activation and release of pro-inflammatory and pro-coagulatory cytokines has been shown during the aura phase [20], but further studies have failed to show consistent changes in vascular reactivity during the aura and a subsequent causal relationship with ischemia [21, 22]. A higher prevalence of patent foramen ovale (PFO) has been reported in migrainous individuals versus controls. The significance of this co-occurrence is still under investigation. [23]

Evidence that cerebral ischemia can manifest as a migraine aura further confounds the diagnosis of migrainous infarcts and their pathophysiology. Brain ischemia may cause prolonged neurological signs mimicking migraine aura and may trigger cortical spreading depression, producing aura symptoms [24]. Another link that connects brain ischemia and migraine is microemboli: a study documented CSD in

response to microemboli injected in the arterial circulation of rodents; the response was more pronounced in rodents showing ischemic brain changes [25]. The study linked the pathophysiological equivalent of migraine aura to arterial microemboli and provided a potential explanation for the increased prevalence of PFO in migraineurs.

**Migraine as a risk factor (Migraine-related stroke)**

It is generally acceptable that migraine, especially migraine with aura, is a risk factor for stroke. Importantly, the overall risk of vascular disease is also increased in migraineurs, as shown in a recent meta-analysis of 16 cohort studies by Mahmoud et al. [26]. In this analysis, the overall risk of major adverse cardiovascular and cerebrovascular events, including ischemic and hemorrhagic stroke, myocardial infarction and all-cause mortality, was moderately increased in individuals with migraine, reaching a Hazard Ratio (HR) of 1.42. A cohort study in the Danish population also showed a positive association between the risk of myocardial infarction, atrial fibrillation or flutter, peripheral arterial disease, venous thromboembolism and migraine [27]. Furthermore, a population-based study and a prospective cohort study in women established increased cardiovascular risk in patients with migraine [29, 30]. While the overall cardiovascular risk is increased in individuals with migraine, the coronary and carotid arteries of most migraineurs show less atherosclerotic changes than individuals without migraine [31]. These findings support the theory that migraine-related vascular events are not mediated by atherosclerosis and classic risk factors. The pathophysiology of migraine-related vascular events remains to be elucidated.

Numerous studies showed increased risk of stroke in individuals with migraine. Five meta-analyses have been published in the last 15 years, all of them showing an increased risk of stroke in migraineurs [26-35]. The estimated relative risk of stroke in individuals with migraine is double compared to migraine-free individuals. This association is stronger for migraine with aura and remains uncertain for migraine without aura. Furthermore, this association is strongest for women, but not men, probably due to confounding factors, such as the overall greater prevalence of migraine in women [32]. Migraine is more prevalent during the fertile period of a woman's life and oral contraceptive (OCP) use is common during this period. An increased risk of thrombotic events in women using OCP's is well-established. A further risk of stroke in migraineurs on the pill is also probable, as shown by a number of studies [38]. This effect seems to be dose-dependent and low estrogen concentrations are associated with a much lower risk, thus making the use of modern contraceptives safer in migraineurs [39].

Young patients have the highest risk of migraine-related stroke, while this risk seems to drop in older individuals [36]. Furthermore, in older patients, migraine is not a risk factor for stroke, unless the headaches started in later life. Another factor conveying increased stroke risk in migraineurs is the number of attacks suffered. Active migraine is associated with increased stroke risk, as shown in a study by Kurth et al, in which patients with weekly migraine attacks had an adjusted HR of 1.93 [37]. Besides frequency, attack severity is not associated with the risk of stroke.

Smoking increases exponentially the risk of stroke in migraineurs. In the meta-analysis by Schurks et al. it was shown that smokers suffering from migraine with aura had an adjusted HR of1.5 [32]. In this meta-analysis, concurrent use of OCPs further increased the risk of stroke, with an adjusted HR of 10. Other lifestyle changes in migraineurs can also have an impact on stroke risk. Migraine is associated with obesity and reduced physical activity, with an unfavorable lipidemic profile and with depression [40-43]. All these factors undoubtedly contribute to the increased stroke risk in migraineurs.

Another mechanism that could be potentially implicated in the increased risk of stroke in migraineurs is their exposure to drugs used to prevent and treat migraine. Both triptans and ergot alkaloids, commonly used in the acute phase of migraine, have vasoconstrictive properties. These drugs are contraindicated in patients with previous stroke or myocardial infarction and in toxic concentrations can lead to ischemic events. Nevertheless, most studies have not found a link between these drugs and stroke in migraineurs [44]. Furthermore, significant vasoconstriction was not shown in the intracranial arteries of migraineurs taking triptans during an attack, whereas vasoconstriction was present in the extracranial arteries [45]. Thus, acute migraine treatments are considered safe and do not increase the risk of stroke in migraine with aura.

Migraine is frequently encountered in the history in young stroke patients. In younger patients, cryptogenic ischemic stroke is increasingly prevalent, with 35-50% of strokes considered cryptogenic after extensive workup. A strong association of migraine with aura with cryptogenic stroke, especially in women, has been shown [46]. This association has in many cases been attributed to the higher prevalence of PFO in patients with migraine with aura [23]. A recent study by Martinez-Majander et al. shows that risk of stroke in patients with migraine is not dependent on PFO status [46]. In this study, the magnitude of right to left shunt, a marker of PFO severity, was associated with the prevalence of migraine with aura,

thus supporting the theory of common pathogenesis of PFO and migraine with aura.

Besides ischemic stroke, several studies evaluated the risk of intracranial hemorrhage in patients with migraine, most of them showing an increased risk. A recent meta-analysis of 16 cohort studies by Mahmoud et al, reported an adjusted HR of 1.43 relative to non-migrainous controls, while a second cohort study in the Danish population showed a HR of 1.94 [26, 27]. Contrary to ischemic stroke, the presence or not of aura doesn't seem to play a significant role in this association. Young women have higher risk both for intracranial hemorrhage and brain ischemia [28].

Besides acute symptomatic stroke, migraine is associated with neuroimaging abnormalities. These include white matter abnormalities (WMA), silent infarct-like lesions and grey or white matter changes. WMA are detected in 4-59% of patients with migraine [47]. A more robust association with migraine with aura exists, while their presence in migraine without aura is disputed [48]. They are not specific for migraine and their etiology or clinical significance remain uncertain. In a study no association was found between WMA and cognitive decline, while another study found higher stroke risk in patients with increased WMA burden [49, 50]. Silent infarct-like lesions are described in migraineurs as small, discrete, round or ovoid lesions in the posterior circulation and especially the cerebellum [51]. Some studies have also identified silent infarct-like lesions in the deep white matter and the basal ganglia [48]. They are not associated with cognitive decline, while their presence signifies increased cardiovascular and cerebrovascular risk [48-52].

Primary prevention of stroke in individuals with migraine with aura is based on risk factor modification. Control of hypertension, treatment of diabetes and hyperlipidemia are essential steps for stroke prevention. Smoking cessation especially in young women using oral contraceptives is imperative. Use of oral contraceptives should be carefully discussed in each case and stopped in women with increased thrombotic risk [53]. While aspirin seems to reduce the frequency of migraine aura and warfarin may reduce the frequency of migraine attacks, the use of antithrombotics is not recommended for primary prevention in migrainous patients [54, 55].

Secondary prevention and treatment after stroke includes use of antiplatelets and modification of risk factors. Some antiplatelets, such as cilostazol and dipyridamole, seem to worsen migraine, by triggering migraine attacks in migraineurs [56, 57]. Beta-adrenergic blockers and calcium-channel blockers have a favorable profile in migraineurs, reducing attack frequency and are preferable for the treatment of hypertension [58]. Statins, besides their effect on lipids, may also influence migraine attacks [59].

## Arteriopathies associated with stroke and migraine

Hereditary disorders may be associated with migraine and cerebral ischemia. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes (MELAS) have been extensively studied. Beyond these two disorders, other syndromes that commonly present with both ischemic stroke and migraine include retinal vasculopathy with cerebral leukodystrophy (RVCL) and hereditary infantile hemiparesis with retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL). [60]

CADASIL is an autosomal dominant angiopathy, caused by mutations in the NOTCH3 gene on chromosome 19. The mutation of the NOTCH3 protein leads to vasculopathic changes predominantly involving small penetrating arteries, arterioles, and brain capillaries. Almost half of affected individuals report migraine with aura, in most being the initial manifestation starting at early 30s. In most cases aura symptoms are typical, but about 50% of the patients experience atypical manifestations, such as hemiplegia, confusion, or long-lasting neurologic symptoms. Ischemic and less frequently hemorrhagic stroke and TIAs affect 85% of these patients, usually at a median age of 50 years [61]. Multiple strokes, cognitive decline, psychiatric symptoms and dementia follow. [62, 63]

MELAS is a maternally inherited mitochondrial disorder characterized by encephalopathy, myopathy, stroke-like episodes and migraine-like headaches. In patients with MELAS stroke-like episodes lead to hemiparesis, hemianopia, or other neurologic symptoms, with atypical imaging characteristics. Headaches are common and can either mimic migraine or be the presenting symptom of stroke-like episodes, leading to diagnosis of migrainous stroke. [64]

RVCL is a much rarer disorder that presents with retinal vasculopathy, migraine without aura, cognitive changes and stroke-like episodes with focal neurologic symptoms. Besides the central nervous system and the retina, vasculopathy is also present in other systems, such as the liver, the gastrointestinal system and the kidneys. In late stages, imaging of the central nervous system may show enhancing mass lesions, potentially confounding this diagnosis. [65]

Understanding the complex genetic and pathophysiologic mechanisms underlying these disorders can unveil the vascular changes involved in migraine, leading to better understanding of the relation between migraine and the acquired vasculopathies.

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# CLUSTER HEADACHE: A REVIEW

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**Abstract**

There is growing interest in biomedical literature over the past few years regarding Cluster headache, this underdiagnosed primary headache that is the most common of Trigeminal Autonomic Cephalalgias. This review provides the essentials to diagnose and treat Cluster headache, which presents most often with a typical head pain accompanied with ipsilateral autonomic nervous system features that constitute the episodic and chronic form of the disease. Important lifestyle risk factors and scales to assess the impact in sufferers' quality of life are reviewed alongside with a synopsis of the pathophysiology background. Furthermore, we highlight the improvements made in early diagnosis due to the growing awareness of healthcare providers and the evolving therapeutic repertoire that includes nowadays a monoclonal antibody and a handheld neuromodulation device amongst traditional agents.

**Key words**: cluster headache, pain, autonomous nervous system, early diagnosis, treatment

Cluster headache (CH) is a unique clinical syndrome amongst the primary headaches, classified as a Trigeminal Autonomic Cephalalgia (TAC). It presents with attacks of severe or excruciating unilateral head pain combined with ipsilateral autonomic nervous system symptoms, causing ictal restlessness and agitation and significant disability to the sufferers [1]. The natural course of the disease in its episodic form (eCH) consists of bouts, that last weeks or even months, followed by pain free periods, whereas its chronic form (cCH) attacks come in longer periods, unremitting for more than a year and in many cases, long term. In cluster headache, stereotypical attacks of rather short-lasting pain sometimes tend to group predominantly at evening hours, following a bizarre chronobiology of Circadian rhythm [1, 2]. Although it is considered a 'rare' disease, compared to the other primary headaches, it affects nearly 1/1000 people, more prevalent to men (3,6:1 ratio) with an age of onset at around 20 up to 50 years old [3,4]. The underlying pathophysiology and the inheritance pattern are not yet fully understood, while treatment consists mainly of non-specific agents and only recently monoclonal antibodies targeting calcitonin gene related peptides (CGRP) have been studied [17]. Despite its striking characteristics, CH remains underdiagnosed and mistreated by physicians, sometimes for years or even decades [5,9].

The 3rd edition of the International Classification of Headache Disorders (ICHD-3) defines intensity of CH pain as severe or very severe when left untreated; strictly unilateral, affecting orbital, supraorbital or temporal sites [1]. Pain intensifies rapidly within 5 to 10 minutes and may last 15 to 180 minutes leaving the sufferer exhausted and vulnerable to another episode [1, 3, 4, 18]. During the pain the recumbent position is most certainly not preferred and unlike patients with migraine, pacing, sitting, or even seeking physical activity and exposure to cold are preferred by patients, as are perceived to relieve the pain [18]. The number of episodes range from once every other day to eight times a day and attacks are accompanied with at least one of the following symptoms or signs ipsilateral to the headache: lacrimation, conjunctival injection, nasal congestion followed by rhinorrhea. Less commonly, forehead and facial sweating, redness and a sense of fullness in the ear. Signs of miosis, ptosis and/or eyelid edema suggesting ipsilateral to pain Horner syndrome may accompany [1-4, 18]. At least five episodes with the above characteristics are required to diagnose CH based entirely on the clinical features, unless they are accounted for by another ICHD-3 diagnosis [1]. The dissemination of bouts in time, when recorded in headache diaries, helps categorize CH forms and demonstrates that the vast majority of patients suffer from eCH, while around 10% from cCH. Chronic cluster headache may start de novo or develop from the episodic form, while some patients with cCH may remit to the episodic form [1-4, 18].

Past medical history of head trauma and social habits such as smoking (>20 cigarettes/day), high alcohol (50-100g/day) and caffeine intake (5-7 cups/day) have been recognized more commonly than expected among CH patients, but the significance is not clarified [6]. A late age of onset combined with longer course of the disease which consists of more than one cluster bout per year or longer lasting

cluster bouts followed by shorter remission periods and more frequent sporadic attacks are well known predisposing factors for relapsing to cCH. On the other hand, use of prophylactic treatment has been shown to favor swinging back into eCH [5, 6].

Several studies hitherto have tried to shed light to the mystery of why this so unique clinical syndrome remains underdiagnosed for so long [5, 7, 9]. Delays in diagnosis are present worldwide and vary from country to country with the mean time to correct diagnosis in UK estimated in 2,6 years, in Spain 4,6 years, in Italy and East European countries 5,3-6,4 years, while data report that the median time in Greece was 1 year (range 0-7) only when the diagnosis made after the 2010. Before 2000, patients waited patiently for a median time of 13 years (range 0-45) [5,9]. Migraine, trigeminal neuralgia and sinusitis were amongst the common misdiagnoses made by general practitioners, ENT specialists, ophthalmologists, dentists or even neurologists or neurosurgeons [5,9]. Overall, in Greece patients with CH were shown to have consulted a median number of 2-5 clinicians before the correct diagnosis, while even neurologists missed the diagnosis in a notable 40% of the patients evaluated [5]. Nowadays, increasing information shared on the internet, social media, podcasts and patient groups have raised awareness about the disease, leading to a considerable number of cases of self-diagnosis by the sufferers. Early onset of the disease, side sifts between or within bouts, location of pain in "atypical" areas such as in the jaw, cheek, lower teeth or ear, presence of photophobia, absence of restlessness and absence of autonomic features may lead to this diagnostic delay [5, 9]. In some cases, the nature of the disease per se, and mainly the short-lasting attacks that tend to cluster and may disappear for quite some time from bout to bout could explain why some patients do not seek promptly expert care. Nonetheless, mis- or late diagnosing leads to mistreated patients that may use over-the-counter medications with poor response or use inappropriate substance, such as illicit drugs. In real life, a whole range of alternative remedies are almost always inadequate to handle the pain caused by cluster headache and without expert supervision, futility seizes the patients that experience the detrimental effects of the condition in their socioeconomic aspects of their life as years pass by [5, 9].

Quality of life (QoL) and Disability surveys using scales have evaluated the impact of the disease in daily activities and mental health [14, 15]. Only rather recently (2016) the Cluster Headache quality of life scale (CHQ) was published. It contains 28 items addressing the restriction of activities, impact on mood and interpersonal relationships, anxiety, and lack of vitality while previous studies failed as they were hospital- based rather than population- based and not sensitive to clinical changes [15]. Although patients underwent surgical procedures for CH that alleviated pain and reduced weekly attacks, QoL improvements were not statistically significant [14]. Absence of CH-guided Disability scales obliges researchers to use either generic or migraine-specific assays like the Migraine Disability Assessment (MIDAS) and the Headache Impact Test (HIT-6) which are short questionnaires that address the negative impact of headache the past 3 months and 4 weeks, respectively [13, 14]. Either one shares its own faults given the fact that a bout may last for only a month and MIDAS requires a long recall period of symptoms. HIT-6 score >60 reflects the severity and the need for treatment though its 3rd question: *"When you have a headache, how often do you wish you could lie down?"* is clearly not designed for the CH patients [13, 14].

Apart from identifying common environmental factors among the sufferers, the understanding of CH pathophysiology may help unmask any genetic predisposition. Recent systematic reviews suggest that while the majority of the cases are sporadic, 6,3% appear to be familial and first-degree relatives of CH patients encounter 5-18 times higher risk of developing this disorder compared to the general population. Studies evaluating single nucleotide polymorphisms (SNPs) and genome- wide association studies (GWAS) revealed the role of HCRTR2 and GNB3 gene-containing SNPs but none of them were significantly associated with CH [10, 11, 12].

The circannual periodicity of the attacks points for a pathophysiological involvement of hypothalamus, the location of first order autonomic neurons who mediate sleep-wake cycles via the suprachiasmatic nucleus. Imaging studies genuinely show the activation of ipsilateral hypothalamic gray matter during the attacks but it is enigmatic how hypothalamus contributes to the pathophysiology [10, 11, 12]. Another culprit is thought to be the trigemino- autonomic reflex which is elicited via efferent neurons of the superior salivatory nucleus that synapse in spheno-palatine ganglion (SPG) and the facial nerve supplying parasympathetic innervation to cranial vasculature and glands [10]. The trigeminal nerve serves as the afferent branch to converge at the trigeminal ganglion (TG) and project back to the trigeminal nucleus caudalis (TNC). Whenever this reflex activates, neuropeptides like CGRP, vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP/ADCYAP1) increase in cranial blood stream [10, 11, 12]. CGRP and its receptors are found in abundance in the central nervous system, especially the posterior Hypothalamus, the trigeminovascular system and the Aδ-, C- fibers involved in pain perception [17]. Presence of CGRP in the TNC alters neuronal activity lowering the activation threshold,

thus contributing to the nociception of pain [17]. PACAP on the other hand greatly increases CGRP release in lamina I/II of TNC, propagating pain [10]. Neurogenic inflammation is the result of vasodilation, plasma protein extravasation, glial and mast cell activation in an unclear hypothalamus mediated response that supports both the periodicity and the profound autonomic activation during the pain [10, 11, 12].

Cluster headache symptoms are not always benign and primary. Ekbom's classic observation of CH symptoms in patients with ipsilateral internal carotid artery stenosis contributed to rule out this secondary headache [8]. In the following years, a large number of pathologies have been associated with secondary cluster headache and a thorough investigation is usually warranted at first appearance of cluster headache symptoms [19].

Treatment of CH is traditionally divided into three categories: acute, bridging and preventive therapies [3, 7]. First presented in a study of 1985, the well-established (level A evidence) use of high-flow (12L/min) concentrated oxygen when provided through a non-rebreather mask can usually terminate the attack within 20 minutes [16]. Recent data from the largest CH survey performed hitherto, updated the effectiveness that reaches up to 44% for "completely effective" result, although there are reported implications regarding the difficulty in obtaining the particular treatment as it is hard to find (apart from the hospitals) and not always compensated for home use by the insurance companies [16]. Comparable effectiveness is shown with 6mg subcutaneous injection of sumatriptan, a serotonin receptor agonist for 5-HT1B and 5-HT1D, completely relieves symptoms in 43% of patients within 15 minutes [3, 7, 16]. Zolmitriptan 5mg nasal spray (level A),10 mg nasal spray (level A) and sumatriptan 20gm nasal spray (level B) can be a plausible alternative to injections wherever this formulation is available. Dihydroergotamine intramuscular injection and cafergot/ergotamine tablets shared intermediate effectiveness and intermediate side effects. Intranasal capsaicin or lidocaine and the newest entry of intranasal ketamine appear safe but of limited effectiveness acute treatment choices [3, 7, 16]. Last but not least, opioids were only 8% "completely effective" and around 50% "completely ineffective", crystallizing that they are a non -viable solution for CH [16].

Bridging therapies consist of short-term interventions that focus on rapidly decreasing the frequency of a sufferer's attacks when a bout starts, regarding the long-term preventive methods require some more time. Oral steroids are traditionally initiated in a tapering dose, while suboccipital nerve block with injected steroids (level A evidence) can be an alternative when systematic use of steroids is contraindicated [3, 7, 16]. Sphenopalatine ganglion (SPG) block with suprazygomatic alcohol solution or radiofrequency ablation (RF) are not widely used nowadays [16].

Preventive therapies aim to reduce the frequency and the severity of pain in the long run and they are used in combination with acute and bridging techniques. Verapamil, a calcium channel blocker that acts in vascular smooth muscle, promotes vasodilation and presents effectiveness in doses ranging 240-960mg per day. Vradycardia, constipation and leg oedema are the main usual side effects [3, 7, 16]. Second- line agents with a lesser potential for efficacy and noteworthy adverse effects, are lithium, used in doses ranging 600-1500mg per day and topiramate [3, 7, 16]. CGRP monoclonal antibody galcanezumab was the first agent in this modern category of preventive treatments to be approved only for episodic CH, when 300mg of subcutaneous injection once monthly proved effectiveness and met safety criteria. Eptinezumab, another CGRP monoclonal antibody, is currently being tested for eCH and cCH [17]. Although IgG antibodies do not cross the brain blood barrier in large amounts, they can still affect the trigeminal ganglion which is left outside BBB and postulate a possible mechanism of action [17]. Devices used for preventive reasons in refractory CH are the non- invasive vagus nerve stimulator (nVNS) and an implantable neuromodulator of the SPG. Deep Brain Stimulation (DBS) of the posterior hypothalamus, especially in the refractory chronic CH, aligns with the suspected pathophysiology of CH, but the relevant studies had to halt [16].

This concise essay was conducted to provide the theoretical background needed to diagnose and treat Cluster Headache, the most common trigeminal-autonomic cephalalgia. Open questions during the clinical evaluation about the nature and the duration of pain, followed by sneaky, closed- type questions about the presence of autonomic symptoms and the mysterious clustering of the attacks followed by pain free periods, will finally unravel this stereotypical deliberating headache that causes significant disability to the sufferers. Exclusion of secondary headaches is most often needed for atypical cases, depicting the brain and its vasculature. Early onset bridging therapy and acute / abortive medication alongside with a long-lasting preventive agent is the mainstay for treatment. The need for psychological support in chronic pain syndromes and lifestyle modifications are "preventive strategies" themselves and should be broached to the patients, pointing out the importance of alcohol avoidance, the thorough management of comorbidities and sleep hygiene Important notice should be given to the patient's adherence to the treatment due to the common phenomenon of medication overuse which can be overthrown by close monitoring via headache diaries and an empathic listener- medical expert. The grow-

ing interest of healthcare providers to acknowledge the key features of the disease pledge to an early diagnosis, with better outcomes and prevention of the chronic form of the disease which is even more disabling and difficult to treat.

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# RECENT ADVANCEMENTS IN TENSION TYPE HEADACHE

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**Abstract**

Tension type headache (TTH) is the most prevalent neurological disorders, with a significant socioeconomic burden. It is characterized by a featureless bilateral headache usually with a tightening or pressing quality and its diagnosis should be followed by the elimination of other primary and secondary headaches. TTH can be classified to episodic form -frequent or infrequent- and chronic form, according to the 3rd edition of the International Classification of Headache Disorders. Pathophysiology of the disorder is still not fully understood but recent findings support the contribution of peripheral mechanisms in generating the pain and central mechanisms in pain chronification. The treatment approach is a process which starts with establishing a good and solid patient-doctor relationship for joined decisions to be made and ends with the selection of a treatment strategy, that usually involves both non-pharmacologic and pharmacologic treatments, either acute or prophylactic.

**Key words**: Tension Type Headache, ICHD-3, Migraine, treatment, pathophysiology

## Introduction

Tension Type Headache (TTH) is the most common headache type globally with a prevalence ranging from 46% to 78% in different studies [1]. Including the non-frequent TTH cases (less than 1 headache per month) the virtual prevalence of TTH may be 100% of the population. Nevertheless, not all cases need medical attention. While TTH is so common with a significant socioeconomic burden there are scant clinical and epidemiological studies, patient awareness and education are insufficient resulting in large numbers of untreated patients. Furthermore, targeted treatment for TTH is still limited, thus reducing patients' compliance. TTH is characterized by mild to moderate severity pain bilaterally in the head. The pain has a pressing or tightening quality and may last form minutes to a week. TTH has no special characteristics like other primary headaches (migraine, cluster headache). This, along with our incomplete knowledge of the pathophysiology of TTH, drove to a somewhat "neglection" of these patients. Recent advancements in migraine pathophysiology and therapeutics highlighted this discrepancy. In this review we aim to provide insight into the epidemiology, pathophysiology diagnosis and treatment of TTH and raise awareness of medical practitioners for this common and burdensome disease.

## Epidemiology – burden

TTH is the most prevalent neurological disease in the European region of the World Health Organization (WHO) and globally according to the Global Burden of Disease study 2017 [2]. The prevalence of TTH was 309,8 million cases in WHO European region and 2,3 billion cases globally with an estimated incidence of 114,4 million new cases in Europe and 882,4 million new cases globally. The respective prevalence for migraine was 195,8 million in Europe and 1,3 billion globally. In the Greek population the prevalence of TTH was calculated as 3.4% (95%CI: 3.4-4.2) with a mean age of 45.4 and 59.5% of them being female [3].

The estimated DALYs (Disability-adjusted life years) for TTH was 7,1 million globally while for migraine 47,2 million DALYs. Hence, it is evident that TTH is the most common neurological disease, but its contribution to the overall burden of neurological disorders in the European Union is 3%, while the respective contribution of migraine is 20% [2]. Regardless of the disability caused though, the impact of both TTH and migraine on Health-related Quality of life (HRQoL) seems to be similar, according to a recent population-based Danish study [4]. This was more evident in Chronic TTH (CTTH) suggesting that headache frequency is related with lower HRQoL indices.

## Pathophysiology

Pain is the subjective experience one feels because of the activation of the nociceptive system; thus, the trigemino-thalamic nociceptive system plays a central role in TTH pathophysiology.

It has been suggested that myofascial tenderness and hardness may be the initial disruption causing the generation of noxious stimuli on the face and head of patients with TTH. Myofascial tenderness and hardness has been found to be increased in both episodic (ETTH) and CTTH patients in days both with and without headache [5]. Furthermore, pericranial muscle tenderness was found to be increased in patients with TTH than in controls [6]. In addition, it has been theorized that chronic pain may lead to abnormal sensitivity of the low-threshold Aβ mechanosensitive fibers –on top of the Aδ and C fibers– who normally carry only innocuous stimuli [7].

The role of peripheral vascular mechanisms in TTH pathophysiology had also been investigated in a somewhat analog scheme of migraine. Although there are some indications that NO and CGRP-induced vasodilation may play a role, further studies are needed to clarify this association [8]. However, it has been found that high levels of nitric oxide induce headache, whereas low levels reduce headache intensity in patients with chronic TTH [9-11]. Other molecules known for their role in other primary headaches like CGRP, substance P and VIP were investigated, but no relation of their levels and the presence of headache was found [12-14].

Through sparce genetic studies it is hypothesized that infrequent ETTH is caused primarily by environmental factors, while frequent ETTH and CTTH are caused by a combination of environmental and genetic factors (15). This conclusion was drawn mainly by twin studies that showed that monozygotic twins and same-sex dizygotic twins had greater difference in concordance rates in infrequent and frequent ETTH [16, 17]. A threefold increase in CTTH risk in first-degree relatives of the cases was found in a family aggregation study [18].

Although very common, the infrequent ETTH has a somewhat minor burden. It is the frequent ETTH and CTTH that carries the most burden on patients and society. Thus, understanding the mechanism of chronification of TTH is crucial. The main theory of chronification is based on the notion that repetitive painful stimulus leads to the sensitization of nociceptive second-order neurons at the level of the spinal trigeminal nucleus and the dorsal horn of the spinal cord [19]. At the same time there may be a reduction of the antinociceptive (descending) effect of supraspinal structures [20]. The overall effect of these changes may lead to increased excitability of dorsal horn neurons and motor neurons of skeletal muscle, [21] producing greater muscle tenderness and lower pain thresholds and therefore increased headache frequency. Furthermore, systemic inflammation may play a role in TTH chronification, since it has been shown that systemic inflammation markers like neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and C-reactive protein were significantly higher in CTTH patients [22].

## Diagnosis – Classification

The lack of specific characteristics of TTH unlike migraine (photophobia, phonophobia, nausea) and Trigeminal Autonomic Cephalalgias (autonomic symptoms), makes the diagnosis a process of eliminating these disorders for a new patient reporting headache. Nevertheless, TTH, and mostly its frequent episodic and chronic type, has some characteristics that appear to be more common in TTH patients. These are the mild or moderate pain intensity, the bilateral location, the pressing or tightening quality and the lack of pain aggravation by routine physical activity [23]. Frequently, patients report a band-like pressing sensation around the head. The 3rd edition of the International Classification of Headache Disorders (ICHD-3) provides criteria for the diagnosis of TTH and further classification in infrequent and frequent ETTH and CTTH sub-types, based mostly on the average headache frequency during a time period (Table 1) [24]. Though uncommon, mild nausea may be a manifestation of CTTH.

Diagnostic approach is primarily based on headache and overall medical history. A headache calendar may be of great help towards this. In terms of classification, when another medical condition is recognized in close temporal relation with the headache onset and it is known that this condition may cause headache, then we must classify this headache as a secondary one, according to ICHD-3 [24]. At the same time, it is of great importance to recognize or eliminate any potential secondary headache disorder which carries great risk for the patient. Although neuroimaging is not recommended during the diagnostic work-up of primary headache disorders[25], it is common in clinical practice to perform some sort of neuroimaging (CT scan or MRI) at least once and indubitably when a red flag for secondary headaches is recognized [26]. Cases of increased intracranial pressure and Medication Overuse Headache (MOH) are easily overlooked, so specific questions regarding the relation of headache with the time of the day, or patients' position and the painkillers used, are of great importance. In case of doubt, a fundoscopic examination may be an easy and much informative examination.

## Triger factors – Risk factors - Comorbidities

A great portion of TTH patients may report one or more triggering factors that precipitate headache. Commonly reported triggers are psychological pressure or anxiety, weather changes, sunlight exposure, dehydration, or certain foods and drinks [20, 27]. Endogenous melatonin status and nutrient status

**Table 1.** Diagnostic criteria of TTH according to ICHD-3

| | Basic characteristics | Frequency (on average) | Special cha racteristics | Nausea and vomiting | Duration | Pericranial tenderness | |
|---|---|---|---|---|---|---|---|
| 2.1 Infrequent ETTH | At least 2 of:<br>1. bilateral location<br>2. pressing or tightening (non-pulsating) quality<br>3. mild or moderate intensity<br>4. not aggravated by routine physical activity | <1 day/month | No more than one: phonophobia, photophobia | No nausea or vomiting | 30 min t o 7 days | Yes | 2.1.1 |
| | | | | | | No | 2.1.2 |
| 2.2 Frequent ETTH | | 1-14 days/month | | | | Yes | 2.2.1 |
| | | | | | | No | 2.2.2 |
| 2.3 CTTH | | >15 days/month | No more than one: photophobia, phonophobia, mild nausea | Neither moderate or severe nausea nor vomiting | Hours to days or unremitting | Yes | 2.3.1 |
| | | | | | | No | 2.3.2 |

**Abbreviations**: ETTH: Episodic Tension Type Headache; CTTH: Chronic Tension Type Headache

of patients with TTH has also been studied. Lower serum 25(OH)D was related to the presence of FETTH [28, 29]. A well-kept calendar may help patients and their treating physician to recognize these factors. Although commonly reported, these triggers factors and their relationship with TTH are not enough studied by randomized or epidemiological trials. On the other hand, many risk factors were reported by cross sectional and longitudinal studies. Examples are young age, female sex, poor self-rated health and few sleeping hours per night [30].

The presence of comorbidities in TTH patients is a well-known feature for clinicians. Many comorbidities were shown to have a greater prevalence in patients suffering from primary headache than the general population. Psychiatric comorbidities and sleep disturbances are the most studied TTH comorbidities. Insomnia, poor sleep quality, excessive daytime sleepiness, insufficient sleep and shift working are some of the sleep disorders that have been reported as having higher prevalence in TTH patients than among subjects without headache [31]. Depression and anxiety are also more prevalent in TTH patients than in headache free patients and are also associated with the frequency and severity of TTH attacks [32]. Arterial hypertension (AH) is another frequent comorbidity of TTH, a fact that led to the description of an AH+TTH phenotype and the study of potential pathophysiologic implications and therapeutic targets [33]. A search in PubMed database for potential TTH comorbidities has recognized a total of 21 disturbances/diseases that have been studied, including Restless Legs Syndrome, Fibromyalgia, Hypothyroidism, neck pain and back pain, temporomandibular dysfunction, tinnitus, and sexual dysfunction (data not published).

## Treatment

Management of TTH patients and primarily infrequent ETTH may start with just reassurance that there is no potential hazard to the patient. By labeling the disorder as a primary headache, patients tend to cope with it more positively and manage to live with it by just using some symptomatic treatment when needed. In more frequent TTH though, reassurance alone is not enough.

Patient education about the nature of the disease and all the coping strategies is of paramount importance. Patients should be aware about trigger management, the life-style modifications required and the available pharmacologic and non-pharmacologic treatments. At the same time trained physicians should get to know their patients, their socioeconomic and psychologic status and establish a potent patient-doctor relationship to form a treatment strategy according to the patients' expectations. This

approach may maximize patients' commitment in non-pharmacologic treatment approaches that may need time to show a positive effect, compliance in pharmacologic treatment and minimize nocebo effect.

### Non-pharmacologic approach

European Federation of Neurological Societies (EFNS) guidelines (34) recommends the use of a non-pharmacologic approach as the first step in headache prevention in eligible patients. Such strategies include psycho-behavioral treatments, physical therapy, and acupuncture. Along with these methods, more recently, mindfulness-based intervention and transcranial magnetic stimulation (TMS) were also considered as alternative therapeutic approaches, yet with limited quality supporting studies [35, 36].

### Psycho-behavioral treatments

EMG biofeedback is the only non-pharmacologic therapy with a class A level of recommendation by the EFNS based on a large meta-analysis that showed medium to large effect on reducing headache frequency [37]. During biofeedback sessions patients are trained to recognize and control muscle tension by continuous feedback about muscle activity.

Cognitive Behavioral Treatment (CBT) and relaxation are less supported by quality studies. The aim of CBT is to provide patients with a learned behavioral strategy to take conscious control over their physiologic response to pain. The same stands for relaxation training, where patients are tought to recognize and control tension in every-day activities by implementing cognitive and behavioral techniques as well as breathing exercises and meditation [38].

Even though these approaches have limited, good quality supporting data, it is recommended that they are used with caution. The excellent safety profile though gives us the opportunity to offer this choice to suitable patients. Patients who exhibit psycho-behavioral problems may benefit by CBT, while relaxation training and biofeedback may benefit more tense patients [34].

### Physical therapy

Many different modalities of physical therapy have been and still are in widespread use by TTH patients, with a great economical cost. These methods include joint manipulation techniques, massaging, trigger point therapy, oromandibular treatment and posture improvement. Yet there is no robust scientific evidence regarding its efficacy. EFNS guidelines recommend the use of physical therapy in patients with frequent TTH [34] and NICE guidelines found no convincing data to make a recommendation for or against manual therapies [39]. A more recent review and meta-analysis found some potential positive effect of manual joint mobilization and supervised physical activity in headache frequency, but with low certainty of evidence, due to risk of bias [40]. Physical activity in general, aerobic exercise and yoga, are choices that clinicians often offer to their patients, but they have not been adequately evaluated, even though there is some evidence of efficacy [41, 42].

### Acupuncture

Acupuncture has better quality evidence than other non-pharmacological treatments to support its effectiveness in reducing headache frequency in ETTH and CTTH patients comparing with placebo/sham intervention or routine therapy [43, 44]. Still, there are some methodological drawbacks in those studies, but the convenient safety profile of acupuncture makes it a choice for TTH patients.

### Pharmacologic approach

### Acute treatment

The mainstay of TTH pharmacologic treatment is an acute treatment, meaning medications used to fight every single episode of headache. Ibuprofen (200-800mg), ketoprofen (25mg) aspirin (500-1000mg), naproxen (375-550mg) and paracetamol (1000mg) are all recommended by the Hellenic Headache Society as class A treatment options for acute TTH. Simple analgesics and non-steroidal anti-inflammatory drugs are also recommended as a first choice according to the EFNS guidelines, while combination analgesics containing caffeine, come as a second choice [34].

Since paracetamol and aspirin are widely used for other indications in different dosages (paracetamol 500mg for other pain syndromes or fever and aspirin 100mg for arterial thrombosis prophylaxis) it is crucial to inform TTH patients that only the recommended dose has shown efficacy for reducing pain intensity.

### Preventive treatment

In the case of frequent ETTH and CTTH, clinicians should offer the choice of a prophylactic treatment. The goal by using a prophylactic treatment is to reduce the headache frequency, measured by headache days per month and monitored by a headache calendar. A reduction of headache by at least 50% is considered as successful treatment, but patients characteristics, comorbidities and expectations should also be taken into consideration.

Amitriptyline, venlafaxine and mirtazapine are currently the available options for TTH prophylaxis. Amitriptyline is considered as first choice drug since its efficacy was documented by multiple studies [45, 46]. Side effects of usual maintenance dose (25-75mg)

are not too common and include drowsiness, dry mouth and weight gain. Slow titration and nighttime intake may reduce some of them. Mirtazapine and venlafaxine where both evaluated as prophylaxis in CTTH in small, randomized trials showing effectiveness against placebo and comparable effectiveness of mirtazapine of that of amitriptyline [47-49]. Major side effects of mirtazapine (30mg) are drowsiness and weight gain and of venlafaxine (150mg) are dizziness and loss of libido.

Selective serotonin reuptake inhibitors citalopram, sertraline, fluoxetine, paroxetine and fluvoxamine showed similar effectiveness as amitriptyline and placebo in reducing headache frequency in CTTH patients [50]. Clomipramine, maprotiline and mianserin are also recommended as third line treatment options based [34, 51, 52]. Botulinum toxin type A showed ineffectiveness for the prevention of CTTH [53].

The duration of prophylaxis in CTTH patients is a matter of debate. EFNS recommends a trial discontinuation of prophylaxis in 6 to 12 months of treatment. Taking into consideration the patients' expectations and comorbidities may dictate the path. The same stands for the overall selection of the prophylactic approach in every individual patient. Personality traits, medical history, age, comorbidities socioeconomic status and accessibility in different medical or physical therapy services, could form a multimodal treatment plan aiming in better compliance and closer monitoring.

## Conclusion

TTH is the most prevalent headache with a significant burden. Even though it is called the "simple headache" it is a complex disease with many environmental, physiological, and psychological factors contributing to its presence. The more stressful everyday life gets, the more prevalent TTH will be with these conditions showing a comorbid association. The pathophysiology of TTH is still not fully understood, but there is convincing evidence supporting both central and peripheral mechanisms.

The diagnosis is made by headache history and by ruling out other types of primary or secondary headache. TTH can be classified in infrequent and frequent episodic TTH and chronic TTH based on average headache days per month, according to ICHD-3 criteria.

The treatment approach is a process which starts with establishing a good and solid patient-doctor relationship so shared decision making can be achieved and ends with the selection of treatment strategy that usually includes both non-pharmacologic and pharmacologic treatments, either acute or prophylactic.

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# NEURORADIOLOGICAL FINDINGS WITH CONVENTIONAL AND ADVANCED MRI TECHNIQUES IN SECONDARY HEADACHES

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**Abstract**

Headache is one of the most common clinical entities that neurologists are confronted with in clinical practice and is associated with a wide spectrum of differential diagnoses. The International Classification of Headache Disorders, 3rd edition (ICHD-III) classifies headache in two main categories: primary headache in the absence of underlying disorder and secondary headache which is attributed to underlying systemic or neurological disease. The classification of headache warrants a detailed patient history and clinical examination, as well as complementary neuroradiological studies, especially when "red flags" point towards secondary headache types that may require therapeutic interventions. The main causes of secondary headache include infections, neuroinflammatory disorders, brain neoplasms, cerebrovascular diseases, and alterations of cerebrospinal fluid (CSF) dynamics. Computed Tomography (CT) studies are primarily used for the acute differential diagnosis of headache, for example in patients presenting with "thunderclap-headache" when subarachnoid haemorrhage is suspected. In the sub-acute setting, however, Magnetic Resonance imaging (MRI) studies are far more sensitive for the delineation of underlying brain pathologies. Besides the use of conventional MRI, advanced MRI techniques, including diffusion imaging, perfusion, spectroscopy and functional MRI, facilitate the early diagnosis of underlying functional, structural, and metabolic changes, while they may be also utilized for treatment monitoring in patients with secondary headaches. In the present review, the most commonly encountered secondary headaches along with associated neuroradiological findings will be presented, focusing on conventional and advanced MRI techniques.

**Key words**: Magnetic Resonance Imaging (MRI), secondary headache, advanced MRI techniques, neuroradiology

# ΝΕΥΡΟΑΚΤΙΝΟΛΟΓΙΚΑ ΕΥΡΗΜΑΤΑ ΜΕ ΣΥΜΒΑΤΙΚΕΣ ΚΑΙ ΠΡΟΗΓΜΕΝΕΣ ΤΕΧΝΙΚΕΣ ΑΠΕΙΚΟΝΙΣΗΣ ΜΑΓΝΗΤΙΚΟΥ ΣΥΝΤΟΝΙΣΜΟΥ ΣΤΙΣ ΔΕΥΤΕΡΟΠΑΘΕΙΣ ΚΕΦΑΛΑΛΓΙΕΣ

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**Περίληψη**

Η κεφαλαλγία είναι ένα από τα συχνότερα συμπτώματα που καλούνται να αξιολογήσουν οι νευρολόγοι στην κλινική πράξη και σχετίζεται με ένα ευρύ φάσμα διαφορικής διάγνωσης. Η Διεθνής Ταξινόμηση Διατα-

ραχών Κεφαλαλγίας, 3η έκδοση (ICHD-III) ταξινομεί την κεφαλαλγία σε δύο κύριες κατηγορίες: πρωτοπαθή κεφαλαλγία απουσία υποκείμενης διαταραχής και δευτεροπαθή κεφαλαλγία που αποδίδεται σε υποκείμενη συστηματική ή νευρολογική νόσο. Η ταξινόμηση της κεφαλαλγίας απαιτεί λήψη λεπτομερούς ιστορικού και ενδελεχή κλινική εξέταση του ασθενούς, καθώς και συμπληρωματική νευροακτινολογική μελέτη, ειδικά όταν συνυπάρχουν ευρήματα που υποδεικνύουν την παρουσία υποκείμενης νόσου που πιθανώς απαιτεί άμεση θεραπευτική παρέμβαση. Οι κύριες αιτίες της δευτεροπαθούς κεφαλαλγίας περιλαμβάνουν λοιμώξεις, φλεγμονώδεις διαταραχές του κεντρικού νευρικού συστήματος, νεοπλάσματα του εγκεφάλου, αγγειακές παθήσεις και μεταβολές της δυναμικής της ροής του εγκεφαλονωτιαίου υγρού (ΕΝΥ). Η διενέργεια υπολογιστικής τομογραφίας (CT) πραγματοποιείται κυρίως σε οξεία φάση, για τη διαφορική διάγνωση της κεφαλαλγίας, επί παραδείγματι σε ασθενείς που εμφανίζουν «κεραυνοβόλο-κεφαλαλγία» και στους οποίους τίθεται η υπόνοια υπαραχνοειδούς αιμορραγίας. Ωστόσο, στην υποξεία φάση, η Απεικόνιση Μαγνητικού Συντονισμού (MRI) έχει μεγαλύτερη ευαισθησία στην αναγνώριση και λεπτομερή αξιολόγηση υποκείμενων αλλοιώσεων του εγκεφάλου. Η συνδυαστική εφαρμογή των συμβατικών τεχνικών Απεικόνισης Μαγνητικού Συντονισμού και των προηγμένων τεχνικών νευροαπεικόνισης, συμπεριλαμβανομένης της απεικόνισης τανυστή διάχυσης, της αιματικής διήθησης πρώτης διόδου, της φασματοσκοπίας και της λειτουργικής Απεικόνισης Μαγνητικού Συντονισμού, διευκολύνει την έγκαιρη διάγνωση και αξιολόγηση μορφολογικών, λειτουργικών και μεταβολικών αλλαγών, όπως επίσης και την παρακολούθηση της θεραπείας ασθενών με δευτεροπαθή κεφαλαλγία. Στην παρούσα ανασκόπηση θα παρουσιαστούν τα συχνότερα αίτια δευτεροπαθούς κεφαλαλγίας και τα νευροακτινολογικά τους ευρήματα, εστιάζοντας κυρίως στις συμβατικές και προηγμένες τεχνικές MRI.

**Λέξεις ευρετηρίου**: Απεικόνιση Μαγνητικού Συντονισμού (MRI) εγκεφάλου, δευτεροπαθής κεφαλαλγία, προηγμένες τεχνικές απεικόνισης Μαγνητικού Συντονισμού, Νευροακτινολογία

## Introduction

Headache is one of the most common symptoms that a patient will experience during his lifetime and one of the most frequent disabling diseases worldwide [1]. According to the International Classification of Headache Disorders (ICHD-III) [2], headache can be classified in primary and secondary headache, with the latter being attributed to underlying causal factors, including infections, neuroinflammatory disorders, brain neoplasms, cerebrovascular diseases, and alterations of cerebrospinal fluid (CSF) dynamics (Figure 1). The differential diagnosis between primary and secondary headache warrants thorough neurological examination, as well as the acquisition of a detailed patient history. If the findings of the clinical examination and patient history are not consistent with primary headache, then secondary headache types are assumed. In such cases, further investigations, including neuroradiological studies are indicated. In clinical practice, a useful mnemonic for the identification of "red flags" that should prompt physicians to indicate neuroimaging studies is SNOOP4 (S: systemic symptoms/signs, N: abnormal findings on neurological examination, O: sudden onset, O: older age at onset above 50 years, P4: positional headache, precipitated by Valsalva maneuver or exercise, progressive headache, papilledema) (Table 1) [3].

The National Institute for Health and Care Excellence (NICE) and the American Headache Society (AHS) guidelines do not recommend neuroimaging studies for patients with normal neurological examination, stable headache without atypical features, that fulfil the diagnostic criteria for a primary headache, while – with the exception of subarachnoid

**Figure 1.** Secondary Headache Disorder Aetiology according to the International Classification of Headache disorders, 3rd edition, beta version

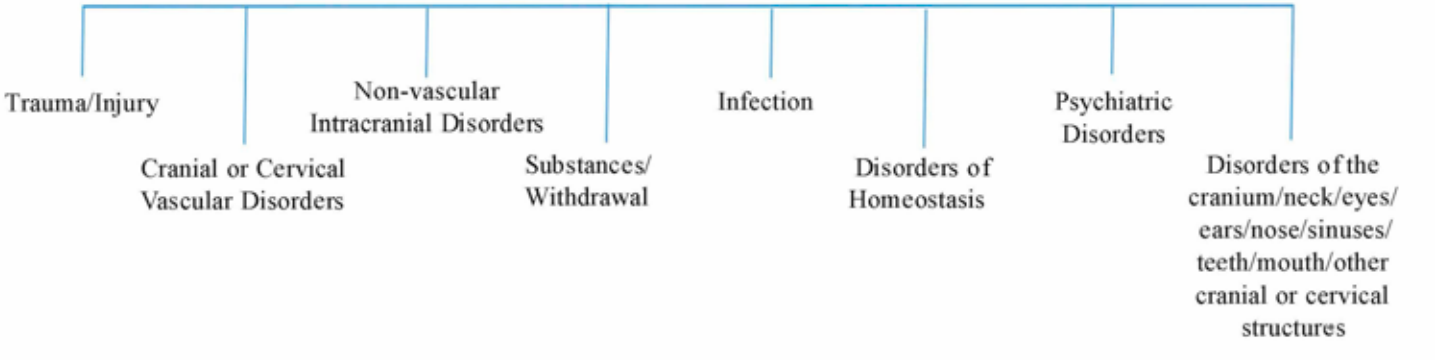


**Table 1.** Red flag signs for the diagnosis of headaches (SNOOP4)

| Mnemonic | Presentation |
|---|---|
| **S**ystemic symptoms | • Fever of unidentified cause, weight loss, chills and myalgia<br>• Malignancy, immunocompromised patient |
| **N**eurological symptoms | • Signs of motor weakness and sensory loss, diplopia or ataxia<br>• Abnormal signs in neurological examination |
| **O**nset sudden | • Thunderclap headache, sudden onset, with peak intensity in <1 minute |
| **O**nset after age 50 years | • Onset after the age of 50 years |
| **P** 4 | • Progressive headache or pattern change<br>• Headache worsening after Valsalva manoeuvre<br>• Postural aggravation<br>• Papilledema |

hemorrhage and in emergency settings – Computed Tomography (CT) should not be performed if Magnetic Resonance Imaging (MRI) is available [4-7]. Conversely, neuroimaging should be performed in all patients presenting with atypical symptoms and signs, for example irregular or new headache patterns; increase in the severity of headache; history of epileptic seizures or head trauma; history of malignancy, active infections, stroke or intracranial bleeding; focal or new neurological deficits; and other "red flags" that may be suggestive of an underlying disorder [5, 8, 9].

Besides the choice of imaging modality (CT versus MRI), the diagnostic protocols also depend on several factors, including patient history, headache pattern, duration, intensity and presence of concomitant neurological signs, as well as depending on whether new-onset or recurrent headache is being investigated [9, 10]. Overall, MRI has a superior sensitivity compared to CT, especially for depicting abnormalities in the posterior fossa, acute ischemic lesions, and mass lesions, while simultaneous performance of an expanded MRI protocol with advanced MRI methods may enable accurate differential diagnosis and treatment planning [11]. It should be noted that the differential diagnosis of headache is practically exhaustive, since headache can comprise an epiphenomenon of many neurological or systemic diseases [1, 2].

Herein, we will review the most commonly encountered causal factors of secondary headache along with the associated neuroradiological findings, focusing on conventional and advanced MRI techniques.

## Secondary headache attributed to cranial or cervical vascular disorder

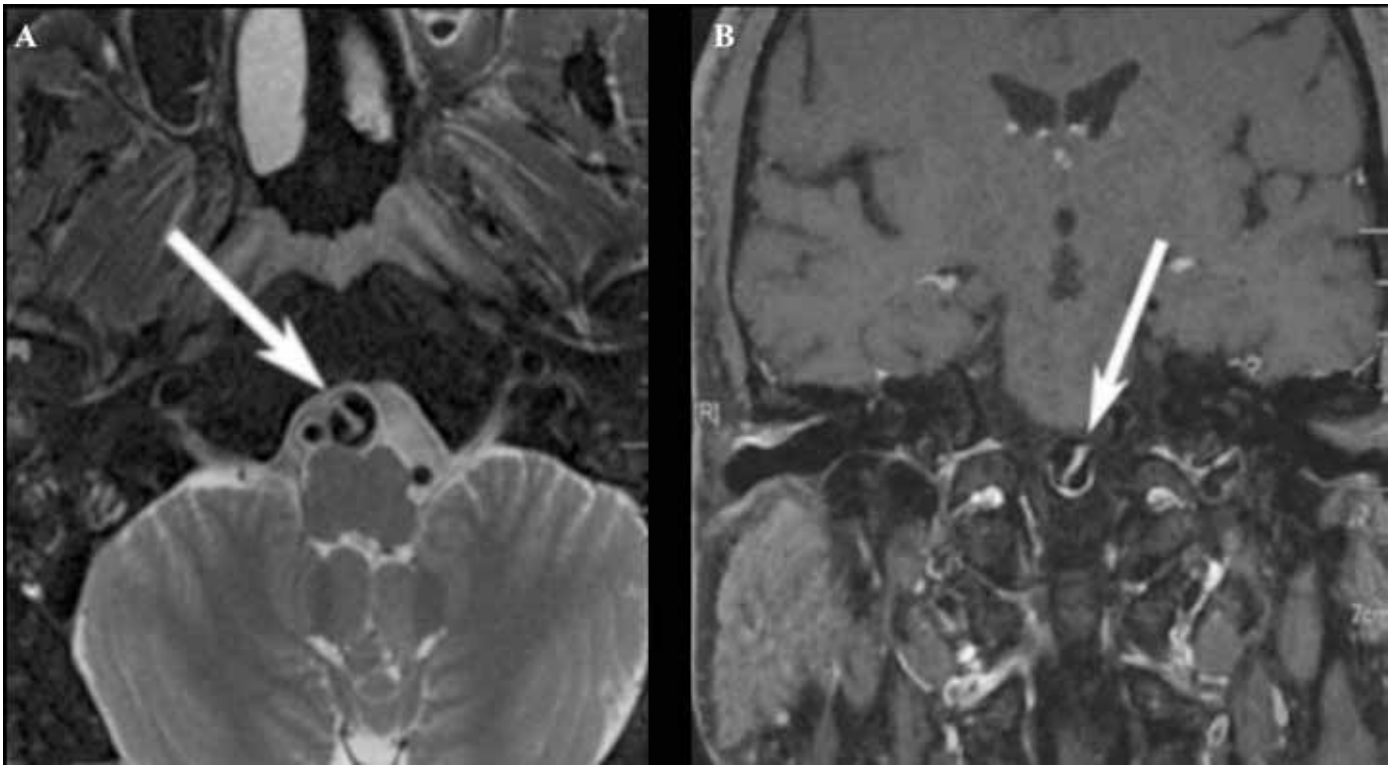
*Craniocervical artery dissection*

Craniocervical artery dissection (CAD) is a frequent cause of ischemic stroke in young and middle-aged adults [12]. Prompt and accurate CAD diagnosis is essential for the identification of the underlying stroke aetiology and prevention of stroke recurrence [13, 14]. The clinical presentation of CAD is variable, ranging from mild symptoms, including neck pain, Horner's syndrome and headache, to severe stroke syndromes [14, 15]. Notably, the headache in CAD is typically ipsilateral to the dissection site [13]. In affected patients, ultrasonography may provide direct or indirect evidence indicative of CAD [16]; in the majority of cases, however, neuroimaging studies including Computed tomography angiography (CTA), MR angiography (MRA), or Digital subtraction angiography (DSA) are required to establish CAD diagnosis.

With respect to CT neuroimaging studies, CTA can provide images of high-resolution and contrast for depiction of the arterial lumen and wall. Two-dimensional (2D) and three-dimensional (3D) reconstruction methods can be employed to construct images comparable to those acquired by DSA, although DSA is still considered the gold standard method for CAD diagnosis [17]. The most typical imaging finding of CAD on CT imaging, with high specificity but low sensitivity, is the so-called "target sign", which is characterized by a narrowed eccentric lumen surrounded by a hyperdense crescent-shaped mural thickening and thin peripheral enhancement [18]. Additional imaging findings suggestive of CAD include the depiction of an intimal flap and a dissecting aneurysm [18].

With respect to MR imaging studies, MRI and MRA have been shown to have an excellent sensitivity of approximately 87-99%, compared with DSA for the diagnosis of internal carotid artery (ICA) dissection. However, the sensitivity of MRA is reduced to 60% for vertebral artery (VA) dissection due to the low calibre of VA and a flow-related enhancement of the paravertebral veins that may be misinterpreted as CAD [19]. Consequently, if VA dissection is suspected,

**Figure 2.** On axial T2W image (A), a dilated left vertebral artery is depicted along with an hyperintense linear intimal flap. (B) On contrast-enhanced 3D black blood T1W the wall of the left vertebral artery, as well as the intimal flap showed marked enhancement, imaging findings suggesting left vertebral artery dissection. (Reprinted with permission from Wang, YM. *et al.* Chinese specialist consensus on imaging diagnosis of intracranial arterial dissection. *Chin Neurosurg Jl* **3**, 30 (2017). https://doi.org/10.1186/s41016-017-0095-2)

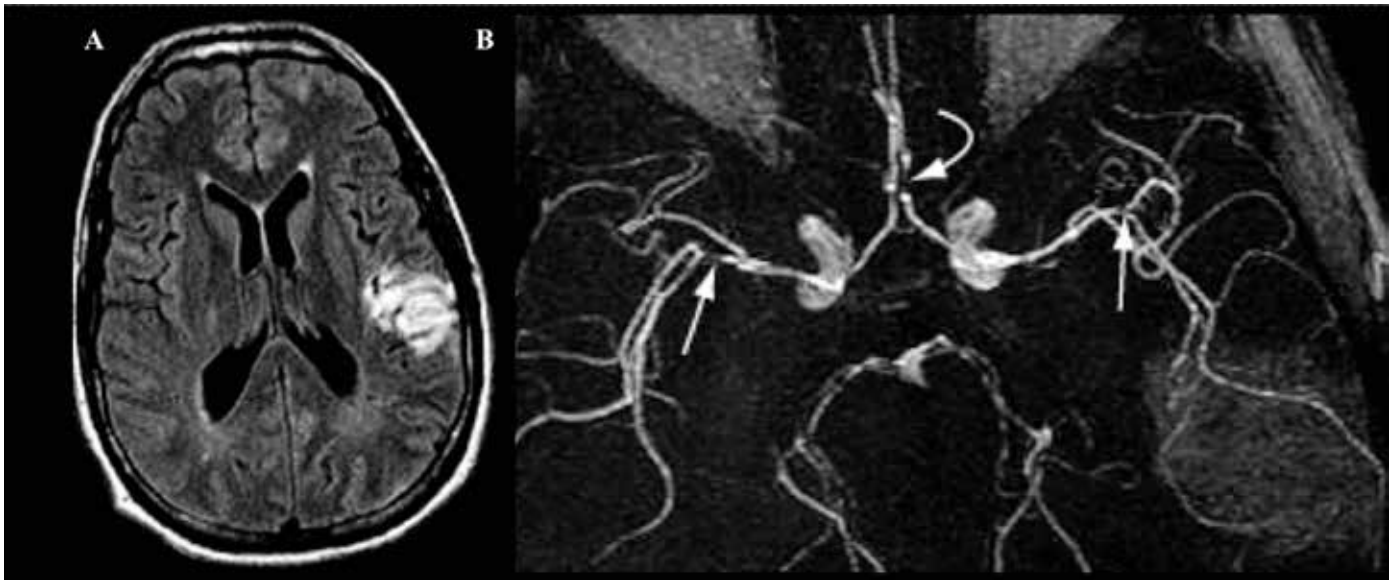



CTA should be performed due to its higher diagnostic sensitivity compared to MRA [19-21]. Notably, contrast-enhanced MRA may provide better results compared to 3D time-of-flight (TOF) MRA [19]. A crescent-shaped intramural hematoma is the most common finding of ICA and VA dissection on MRI. The signal intensity of the hematoma is analogous to the products of haemoglobin breakdown and their paramagnetic effects. In the acute phase, the intramural hematoma may be obscured on T1W fat-saturated images, while in the subacute phase (7 days to 2 weeks post-dissection) the hematoma is depicted with high signal [21]. Additional MRI findings of CAD include narrowed eccentric lumen and increased external diameter of the artery. More recently, heavily T1-weighted flow-suppressed sequences, such as magnetization-prepared rapid acquisition gradient–recalled echo (MPRAGE), have also been implemented to detect carotid intraplaque haemorrhage in CAD [22]. Moreover, 3D black-blood fat-saturated T1W sequence has been shown to have high sensitivity for the depiction of intramural hematoma [23]. Additionally, vessel wall imaging sequences may be performed in addition to TOF-MRA, in order to assess the luminal calibre. Finally, a 3D simultaneous non-contrast angiography and intraplaque haemorrhage (SNAP) MRI technique has been recently introduced to provide information both regarding the arterial wall and the arterial lumen in a single scan [23, 24] (Figure 2).

*Vasculitis*

Headache may be the only presenting symptom of giant cell arteritis (GCA), and GCA should always be considered in elderly patients (especially women) presenting with new-onset headache [25]. GCA –also known as temporal arteritis– is a granulomatous vasculitis mainly affecting medium and large sized arteries. The main histological feature of GCA is granulomatous arterial inflammation caused by lymphocytes, histiocytes, and multinucleated giant cells [26]. It must be mentioned that in GCA, unaffected areas may be noted between the inflamed arterial sites, which are known as "skip lesions". Biopsy results are false-negative in approximately 8-28% of GCA patients, especially when biopsy is taken from normal-appearing lesions, i.e., not guided by imaging studies [27]. Although temporal artery biopsy comprises the gold standard for GCA diagnosis, neuroimaging studies are increasingly used in clinical practice for GCA diagnosis, for biopsy plan-

**Figure 3.** (A) On axial FLAIR image, a high-intensity lesion in the white matter on the left temporal lobe is depicted, which is a non-specific finding. (B) MR angiography shows multifocal segmental narrowing of right and left middle cerebral artery and left anterior cerebral artery(arrows), suggesting primary angiitis of the CNS (PACNS)




ning, as well as for treatment monitoring [28]. Advanced MRI sequences, such as the 3D black-blood fat-saturated T1W sequence, facilitate the depiction of mural inflammation and allow measurement of the mural thickening and quantification of the contrast enhancement [29]. Furthermore, TOF MRA can depict the luminal diameter, which appears decreased in regions affected by GCA [30]. The combination of the two aforementioned MRI techniques has been shown to have a high sensitivity and specificity for GCA diagnosis, of 80% and 100% respectively compared to the gold standard of temporal artery biopsy [30].

Headache, when accompanied by encephalopathy, may also be a presenting symptom of primary angiitis of the central nervous system (PACNS). Although PACNS is a rare nosological entity, high clinical awareness is warranted in patients presenting with headache and encephalopathy, and atypical ischemic strokes. Ischemic infarctions are noted on neuroimaging in approximately 53% of PACNS cases [31]. Conventional MRI techniques reveal multiple infarctions, which are typically bilaterally located, in various stages of healing, of variable size and affecting different vascular territories [32]. Vessel wall MRI (VW-MRI) can also be applied for the diagnosis of PACNS, depicting prominent vessel wall enhancement [33]. Notably, PACNS should be differentiated from vasculitis that may be secondary to other causes, including infection, systemic disease, malignancy, drug use, or radiation therapy, and histological confirmation is required for definite PACNS diagnosis [32, 34] (Figure 3).

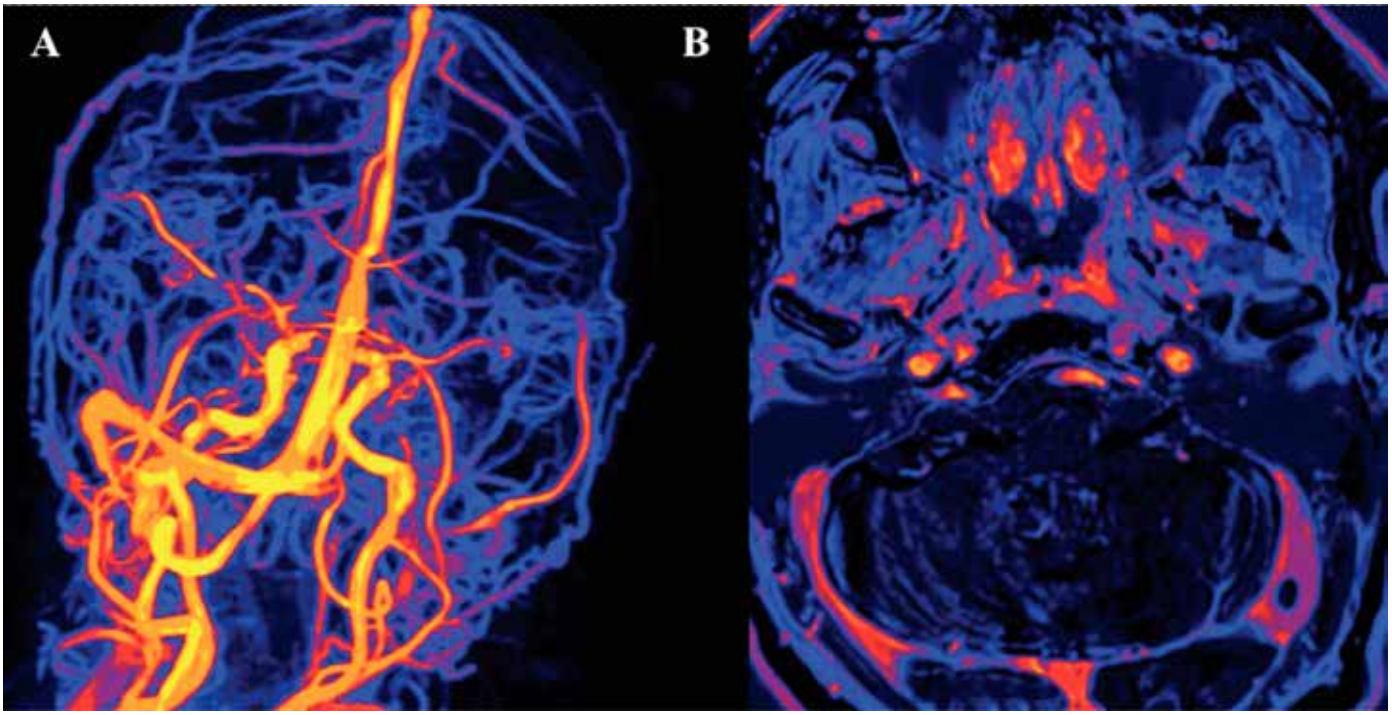
*Cerebral venous sinus thrombosis (CVST)*

Headache, focal neurological deficits, epileptic seizures, intracranial hypertension and encephalopathy comprise frequent clinical presentations of CVST, with varying intensity depending on the site of venous thrombosis [35]. Headache is present in more than 85% of CVST patients [36, 37]. Although CVST-associated headache may be accompanied by nausea, vomiting, papilledema, and visual disturbances, in some cases headache may be the only CVST presenting symptom. The spectrum of headache patterns associated with CVST is very wide, but the most commonly encountered is subacute-onset headache with rapid worsening, that may mimic subarachnoid haemorrhage, migraine or intracranial hypertension [38, 39].

Neuroimaging studies comprise the cornerstone of CVST diagnosis and aim to answer: (1) whether there is evidence of cerebral venous occlusion; (2) whether there are findings of parenchymal or other intracranial lesions; (3) which is the underlying cause of CVST [40, 41]. In more than 85% cases of CVST cases, a prothrombotic risk factor or a direct underlying cause can be identified, while multiple CVST causes can be found in approximately 1/3 of cases [35]. Furthermore, neuroimaging studies are additionally used for the follow-up of CVST patients, depicting the venous recanalization and treatment response, and for excluding CVST complications or recurrence.

CT is considered as first-line imaging modality for patients admitted to the emergency room (ER) with suspected CVST. Non-enhanced brain CT may depict

**Figure 4.** A 65-year-old male presented with headache. (A) Time-of-flight (TOF) MR venography shows absence of normal flow signal in the left transverse and left sigmoid sinuses, indicating CVST. (B) Axial contrast-enhanced MRV depicts a filling defect in the left transverse sinus, corresponding to a nonenhanced ovoid thrombus




hyperdense thrombus in the dural sinus ("dense triangle sign") or in cortical veins ("cord sign"), but in up to 2/3 of CVST cases the findings of non-contrast-enhanced brain CT are false negative [42]. By contrast, CT venography (CTV) has a 95% sensitivity for CVST diagnosis compared to DSA as the gold standard [43].

In CVST patients, MRI findings are time dependent, as the signal intensity of the thrombus may vary according to the haemoglobin degradation [44]. Phase-contrast and time of flight MRV may detect CVST, but each technique has limitations and disadvantages (Figure 4). Contrast-enhanced MR-venography (MRV) is highly accurate in diagnosing CVST at all stages, including the chronic stage compared to any other type of MRV [45]. Digital subtraction angiography (DSA), albeit considered the gold standard for CVST diagnosis, is nowadays reserved for patients that may require endovascular treatment [46].

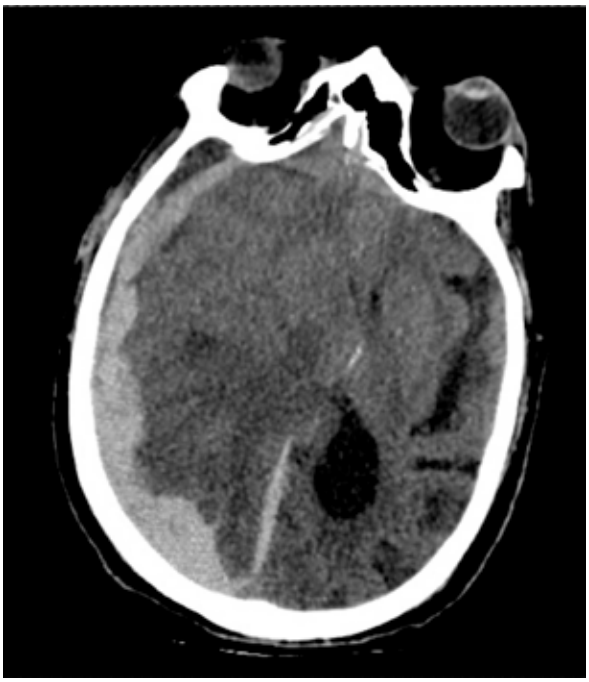
Parenchymal abnormalities as consequence of CVST include venous infraction, intraparenchymal and subarachnoid haemorrhage, hydrocephalus due to impaired CSF absorption and brain edema are better assessed on MRI rather than on CT [47]. Use of Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) map can facilitate the distinction between vasogenic and cytotoxic brain edema, that may coexist in CVST [48, 49]. Finally, it should be stressed that neuroimaging is important for exclusion of CVST recurrence which affects approximately 12-13% of patients [50].

*Subarachnoid Haemorrhage (SAH)*

Thunderclap headache is a characteristic manifestation of subarachnoid haemorrhage (SAH). Typically, patients describe this type of headache as the "worst headache of their life" [37]. SAH is classified in traumatic and spontaneous SAH. Among the causes of spontaneous SAH, rupture of intracranial aneurysms accounts for up to 85% of SAH cases [51]. The remaining 15% of SAH patients have no discernible cause of bleeding [52]. Crucially, perimesencephalic SAH is a distinct type of SAH, that accounts for 5% of all SAH cases and is related to underlying venous drainage anomalies rather than underlying aneurysms [53].

On neuroimaging, the distribution and epicentre of SAH can indicate the localization of a ruptured aneurysm or other underlying pathologies that may precipitate non-aneurysmal SAH. For example, the presence of convexity SAH sparing the basal cisterns, the Sylvian fissure, the interhemispheric fissure or the ventricles with additional imaging findings of microbleeds and cortical superficial siderosis may indicate cerebral amyloid angiopathy as the underlying cause of SAH [54]. With respect to aneurysmal SAH, the most frequent localization of aneurysms in approximately 90% of cases involves the anterior circulation [55].

**Figure 5.** Post traumatic subarachnoid haemorrhage (SAH). Acute subdural hematoma and acute epidural hematoma is depicted on the right hemisphere and along the tentorium cerebelli. Additionally, hyperdense material is seen filling the sulci adjacent to the subdural and epidural hematoma, suggestive of traumatic SAH. Secondary features of mass effects are depicted, including midline shift and right ventricle compression



With respect to CT studies, (Figure 5), in a patient presenting with thunderclap headache it is pivotal to indicate emergent CT scan, that besides native CT should include CTA for exclusion of underlying aneurysms. For the detection of aneurysms >3 mm, CTA –especially using subtraction and three-dimensional reconstructions– has a sensitivity and specificity that approaches 100% and is thus, comparable to that of DSA [56, 57]. Nonetheless, DSA remains the gold standard for the definitive detection or exclusion of underlying intracranial aneurysms, and is superior to CTA for detection of small-sized aneurysms (Figure 6). Moreover, DSA is indicated for patients that may require endovascular treatment.

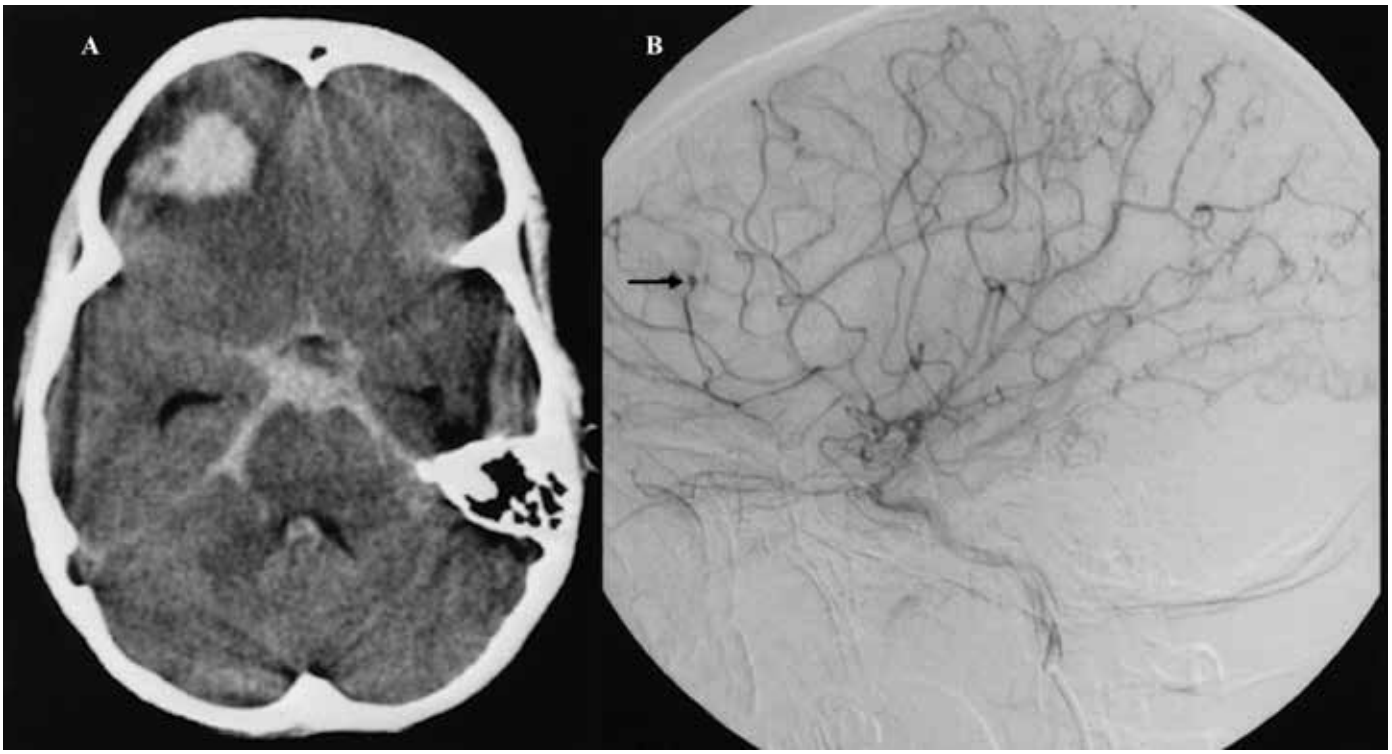
With respect to MRI findings of aneurysmal SAH, the fluid-attenuated inversion recovery (FLAIR) MRI sequence is sensitive for depicting SAH in the first 12 hours, when SAH appears as hyperintensity in the subarachnoid spaces. FLAIR is superior to CT for subacute and chronic SAH, as "aging" hematoma is difficult to capture on CT in subacute and chronic stages [58, 59]. MRA has a sensitivity of approximately 80% for depicting cerebral aneurysms, but its sensitivity is lower for detection of small aneurysms (diameter <3mm in maximum diameter) and aneurysms located at the internal carotid artery and anterior cerebral artery [60]. The sensitivity of gradient echo (GRE) sequences differs between the different SAH stages, ranging from a 94% sensitivity during the early SAH stages (up to 4 days), to a 100% sensitivity beyond the acute SAH stage (after 4 days from index event) [61]. Importantly, DWI may demonstrate early ischemic changes associated with SAH or delayed ischemic changes associated with vasospasm, which may complicate up to 20% of SAH cases [62]. MR perfusion can be a useful tool for the diagnosis of cerebral ischemia and evaluation of the cerebral blood flow [63]. Besides the acute SAH diagnosis, it is important to note that MRI has an additional role in excluding concomitant aneurysms, that are not ruptured or may have undergone subclinical rupture (as indicated by haemoglobin products depicted on GRE sequences), as well as for treatment follow-up (i.e., in patients with vasospasms undergoing vasodilator therapy, or patients with aneurysms treated with non-ferromagnetic clips or endovascular therapy).

*Reversible Cerebral Vasoconstriction Syndrome (RCVS)*

RCVS is clinically characterized by thunderclap headache, which is pathophysiologically related to reversible vasoconstriction of the cerebral arteries. The headache is mainly localized in the occipital lobes, but in some cases may be diffuse. RCVS may be noted in the post-partum period, while typical risk factors include the use of vasoactive substances and drugs (i.e., marijuana, cocaine) [64]. Diagnostic criteria for RCVS have been suggested with 98-100% specificity including: (i) thunderclap headache with periodical recurrence; or (ii) single thunderclap headache either without evident abnormality on neuroimaging or with neuroimaging evidence of watershed infarct/vasogenic edema; or (iii) abnormal angiographic findings with normal neuroimaging and no headache [65]. At symptom onset, neuroimaging may be normal in approximately 50% of RCVS cases [64]. On neuroimaging, RCVS may be diagnosed based on imaging finding either directly pertaining to vascular narrowing or indirectly to RCVS complications (Figure 7).

With respect to CTA, MRA or DSA studies, findings compatible with RCVS include: smooth tapered narrowing from large to medium-sized arteries with concomitant second-order and third-order branch dilatation, which is the so-called "string of beads" appearance of cerebral arteries [66]. Vessel wall MRI (VW-MRI) may be additionally performed in order to exclude arterial wall enhancement, which is typically not present in RCVS, but may be noted in vasculitis and intracranial atherosclerotic plaques [67]. RCVS complications should also be evaluated using CT or

**Figure 6.** A middle-aged male patient presented with thunderclap headache in the Emergency Room. (A) On axial CT, subarachnoid haemorrhage and intraparenchymal cerebral haemorrhage in the right frontal lobe were noticed. CT angiography did not reveal any aneurysm. (B) On Digital Subtraction Angiography (DSA), a small aneurysm, with diameter less than 3mm, at the right middle cerebral artery was depicted (arrow)




MRI studies, including with decreasing frequency: vasogenic edema (38%), cerebral convexity SAH (22-34%), watershed infarct (29%) or lobar haemorrhage (6-20%) [64, 68]. The typical RCVS course entails resolution of clinical symptoms and neurovascular findings within 8-12 weeks [69].

*Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)*

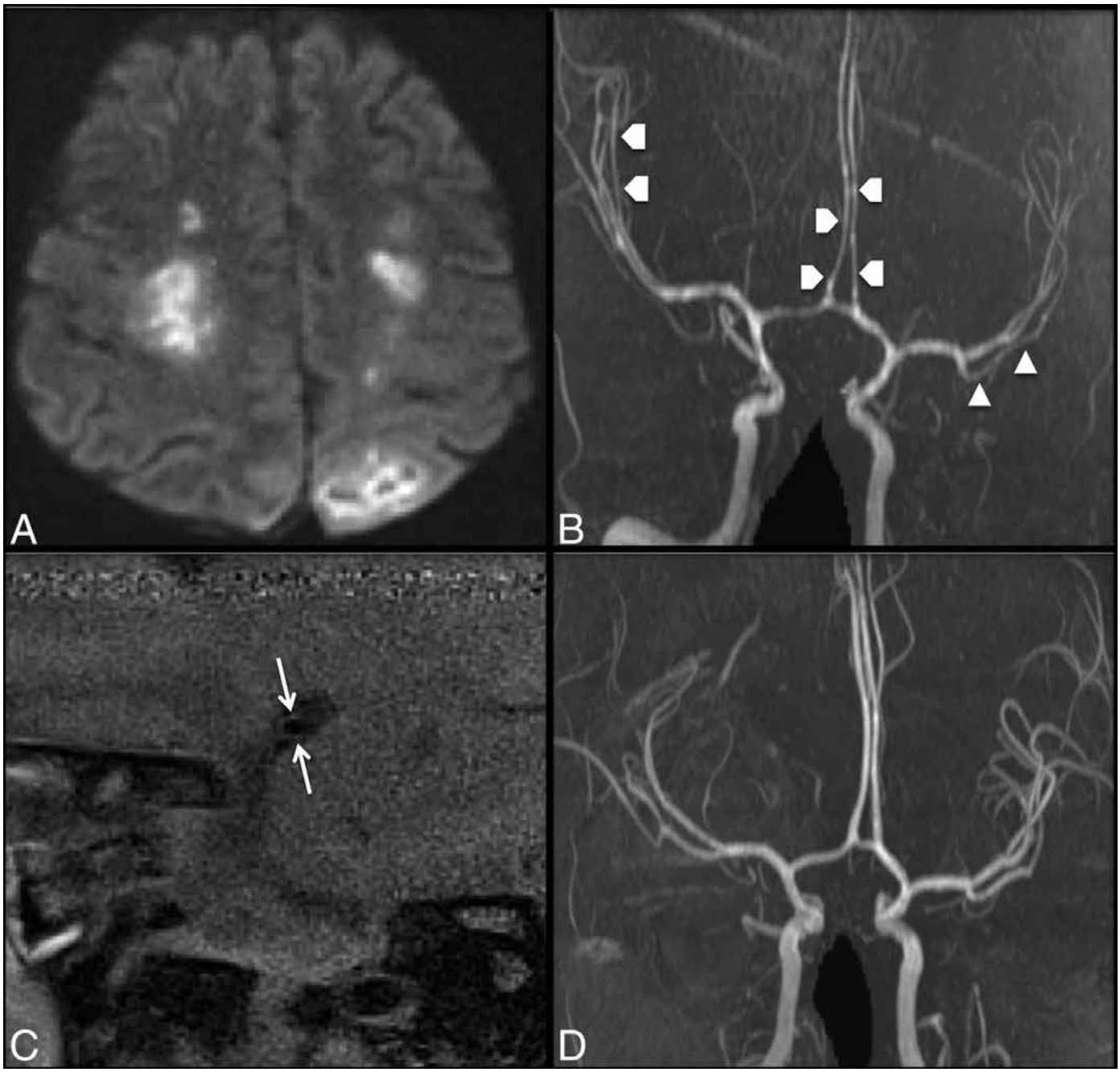
CADASIL is a rare autosomal dominant microvasculopathy affecting young and middle-aged patients, and is characterized by recurrent subcortical infarcts and leukoencephalopathy, migraine with aura and vascular dementia [70-72]. MRI is the gold standard for CADASIL diagnosis, typically revealing three types of lesions in CADASIL patients: i) widespread confluent white matter hyperintensities, with symmetrical and bilateral tendency, which already at early stages involve the anterior temporal lobe and the external capsule; ii) lacunar infarcts; and iii) cerebral microbleeds [73]. Neuroimaging findings, and particularly the white matter hyperintensities may precede the clinical manifestations of CADASIL (Figure 8). Advanced MR techniques may enable early detection of neuronal loss and demyelination, in regions that may appear normal with conventional MRI techniques. ADC histograms, Diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) may assess ultrastructural alterations that may be associated with the clinical phenotype [74, 75]. Also, it has been suggested that quantitative diffusion MRI can offer predictive metrics for assessment of CADASIL progression [75, 76].

## Secondary headache attributed to non-vascular intracranial disorders

*Intracranial Hypotension*

Intracranial Hypotension (IH) is a rare syndrome characterised by decreased CSF pressure < 6cm $H_2O$. A CSF leak along the neuroaxis, in the cervical or thoracic spine in the majority of patients, is the cause of CSF pressure decrease [77, 78]. Typically, IH patients present with a headache with postural pattern, worsening when upright and improving in a recumbent position, with symptom improvement within 15 minutes from lying down. Additional symptoms include vomiting, nausea, vertigo, visual and hearing disturbances and neck pain. According to the causative factor, IH is classified in primary-spontaneous (SIH) and secondary i.e. iatrogenic or traumatic.

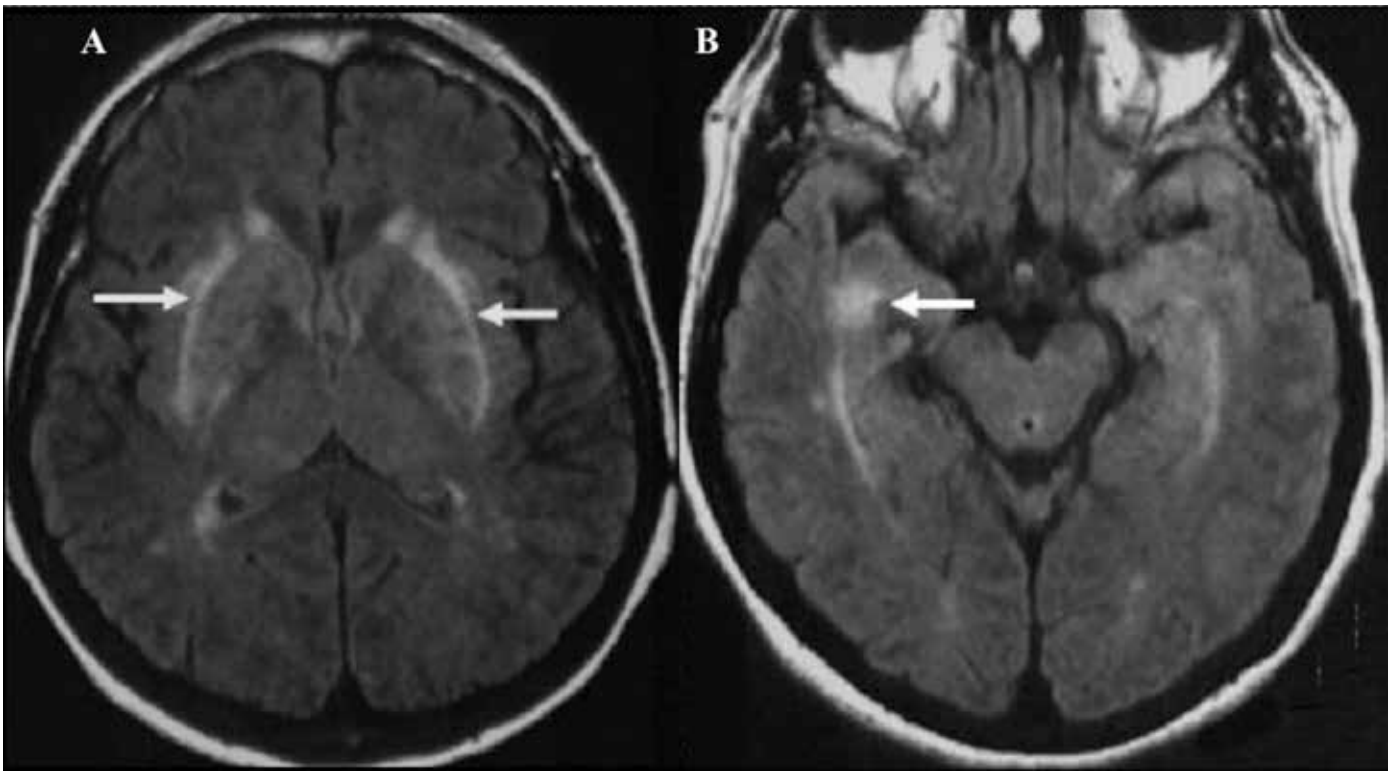
**Figure 7.** A 55-year-old woman who presented with severe headache and developed left-sided weakness. DWI (A) shows multifocal infarcts involving the centrum semiovale and left posterior parietal lobe. On coronal 3D reformatted TOF MRA (B), there is diffuse narrowing of the bilateral middle and anterior cerebral arteries (white arrowheads). Parasagittal postcontrast T1 high-resolution Vessel Wall Imaging (VWI) of the M1 arterial segment of the left MCA (C) shows mild wall thickening and minimal enhancement (similar findings were noted in the right M1 arterial segment, not shown). The patient was diagnosed with RCVS, with subsequent resolution of cerebral vasoconstriction (D)




ICHD-3 has established diagnostic criteria for SIH combining both clinical and radiological findings: i) any type of headache fulfilling the following conditions: headache developed in relation to decrease of CSF pressure; or CSF leakage; or headache leading to the discovery of CSF leak; ii) CSF pressure <6 cm $H_20$ or/and imaging findings of CSF leak; iii) is not attributed to any other ICHD-III diagnosis [78].

The pathophysiological mechanism explained by Monro-Kellie doctrine may help understand the imaging findings of IH [79]. The main imaging findings of IH reflect the alteration of the equilibrium between CSF volume, intracranial blood and brain tissue. Since the brain tissue volume is stable, a decrease in CSF volume will be followed by compensatory increase of intracranial blood. These changes thus, result into

**Figure 8.** On axial FLAIR images, in a 26-year-old patient with family history of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), widespread white matter hyperintensities most pronounced in the temporal lobes are demonstrated. The thalami and pons are also affected



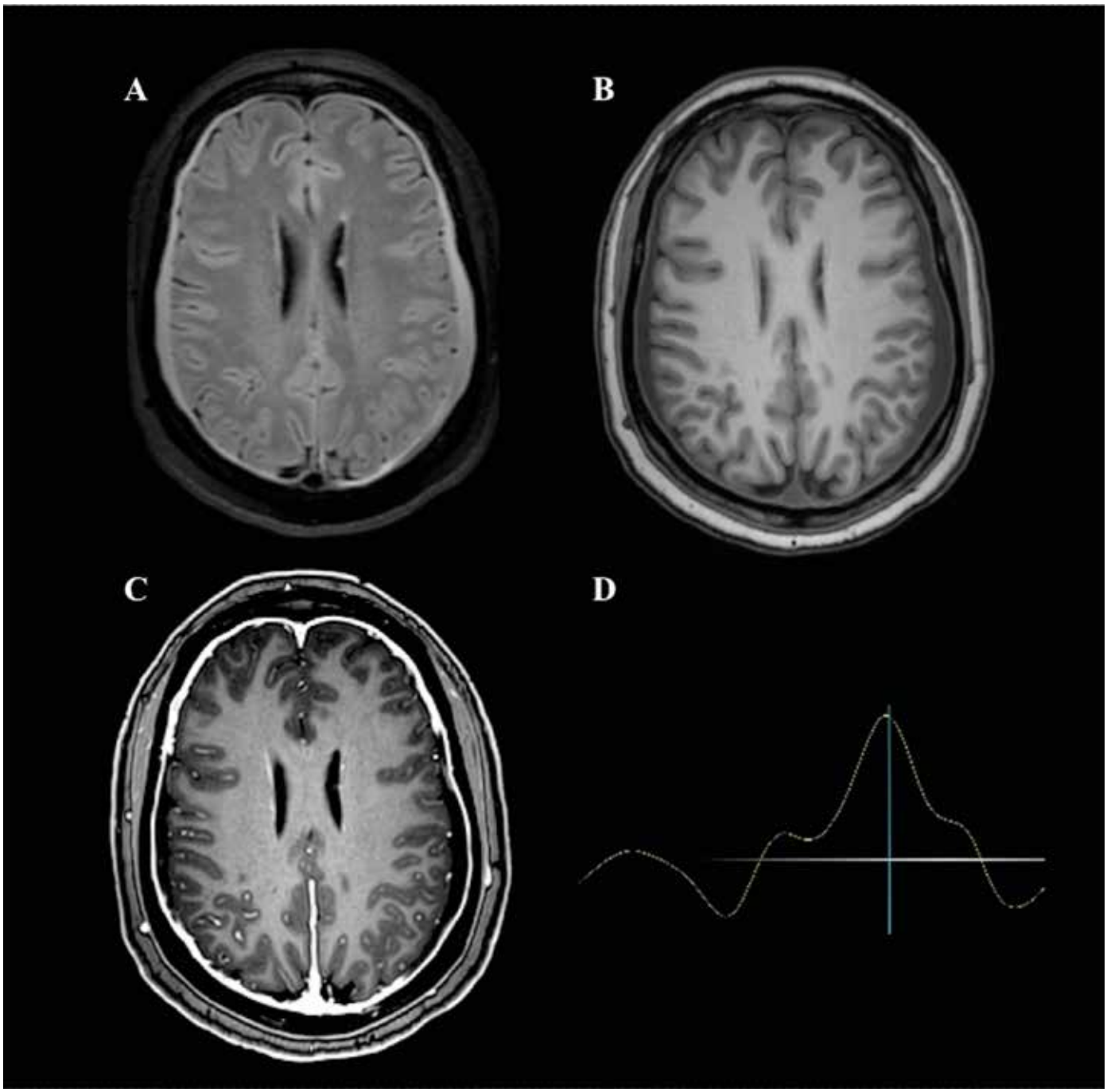

dilatation of vascular spaces, specifically the venous spaces due to their higher compliance [80].

Brain CT can be a helpful tool for the initial diagnosis of IH in the ER as well as in the outpatient setting [78]. Nevertheless, the imaging method of choice for IH diagnosis and treatment monitoring is brain MRI, while intravenous contrast administration is mandatory to depict the typical IH features. It should be noted, that brain imaging may be normal in approximately 20-30% of patients with clinically confirmed diagnosis according to the aforementioned diagnostic criteria proposed by ICHD-3 [78, 81]. Complementary whole spine MRI with intravenous contrast administration has been recommended in patients unresponsive to medical treatment to identify IH and potentially to depict the site of CSF leakage. Although spine MRI can detect in some case the location of CSF leak, CT myelography (CTM) is more sensitive for leak identification [82].Conventional myelography must be performed either when a rapid leak is suspected, which may be obscured on CTM, or when CTM findings are normal. Invasive MR myelography with intrathecal gadolinium administration has a higher sensitivity than CTM for CSF leak depiction, but the intrathecal use of gadolinium still remains off-label [83-85].

During the past years, CSF flow studies on MRI have been increasingly used to assess and quantify pulsatile CSF flow. 2D phase-contrast MRI (PC-MRI) is the most widely used velocity encoding method for CSF flow analysis. Typically, the CSF flow parameters obtained with PC-MRI are significantly lower in IH patients compared to healthy controls (Figures 9, 10) [86]. Moreover, a correlation has been established between CSF flow parameters, headache intensity and CSF opening pressure [86]. Similarly, PC-MRI parameters in patients with spontaneous IH may be used for treatment follow-up [87].

Diffuse pachymeningeal thickening and enhancement is the most common MRI finding in IH patients. The thickening and enhancement is typically smooth and continuous without skip areas. The aforementioned imaging findings are attributed to "leaky" dural microvessels, which have been shown to lack tight connections and enable "spilling" of gadolinium [88]. It should also be mentioned that diffuse pachymeningeal thickening may not be evident in chronic IH cases, which in conjunction with changes in clinical findings (i.e., alteration of the headache pattern) may hinder IH diagnosis [89]. Another common imaging feature in IH patients, affecting approximately 50% of cases, is the presence of hyperintense subdural effusions due to the presence of proteinaceous fluid leaking from the congested dura [90]. Further imag-

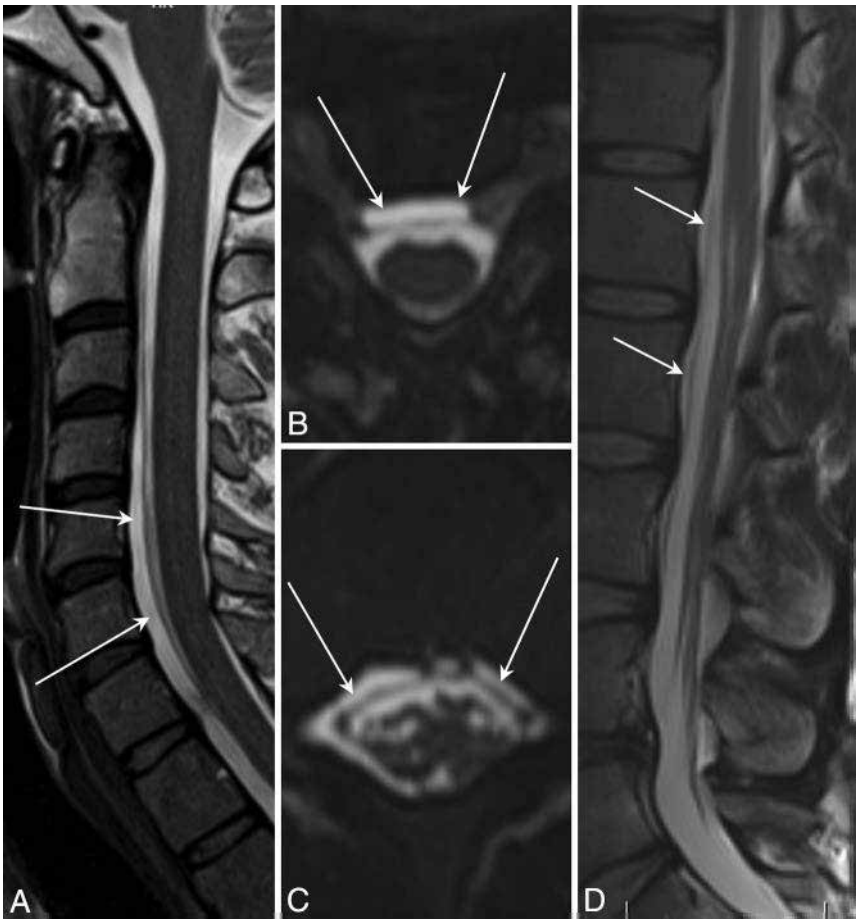
**Figure 9.** A middle-aged female patient 5 days after sinus surgery presented with headache and fever. On axial FLAIR (A) and T1W (B) images, enlarged subdural collections and prominent dural thickening were evident, along with strong pachymeningeal enhancement on post-contrast T1W (C). On 2D phase-contrast MRI (PC-MRI) (D), the CSF flow metrics did not reveal any sign suggestive of intracranial hypotension




ing abnormalities include engorgement of venous structures, enlargement of the pituitary gland, caudal tonsillar displacement and slit ventricles [88].

Spinal MRI, in 67-100% of cases, will show fluid collections-spinal hygromas in the epidural space. Longitudinally, spinal hygromas typically exceed five spinal segments, and are located either anteriorly or posteriorly to the dural sac [91]. Other findings suggestive of IH include engorged spinal epidural veins, circumferential dural enhancement usually combined with intracranial dural enhancement and fluid between the C1-C2 spinous processes. The latter finding is attributed to transudate leakage from the rich regional venous plexus and is considered as a CSF "false-localizing" sign [91].

**Figure 10.** Spinal longitudinal extradural collections. (A), Sagittal T2 FSE. (B), Reformatted axial 3D-T2W images show spinal longitudinal extradural CSF collections (SLECs - arrows) and displaced dura outlined by the CSF. (C and D), Images similar to A and B of the same patient show similar findings in the lower thoracic region

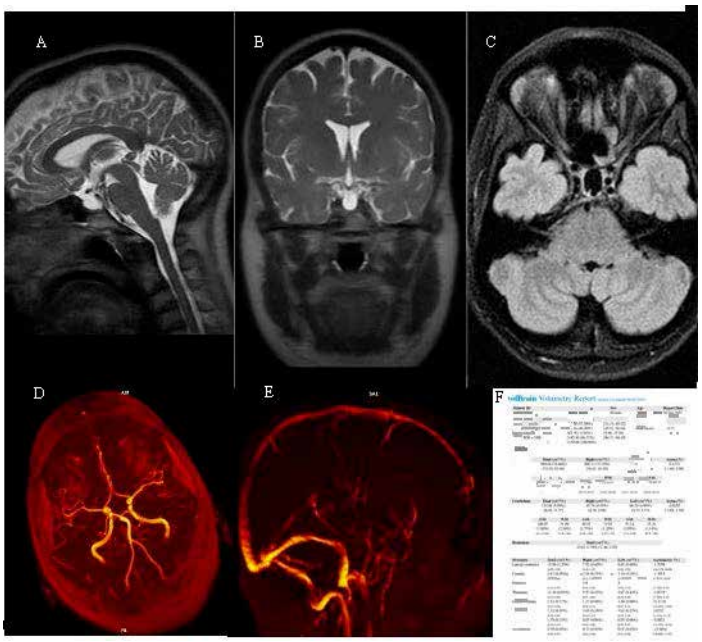



*Idiopathic Intracranial hypertension (IIH)*

IIH, previously known as pseudotumor cerebri, comprises another cause of secondary headache, attributed to elevated intracranial pressure, without evident causative mass or hydrocephalus. Typically, there is a female predominance, with IIH affecting mostly women of reproductive age, with increased body mass index. The most common presenting symptom of IIH is a pressure-like, throbbing headache. Additional clinical symptoms include transient visual obscuration with typical tunnel vision, photopsia, eye pain, pulsatile tinnitus, rarely 6$^{th}$ cranial nerve palsy and papilledema, which warrants ophthalmological evaluation. When lumbar puncture is performed, the CSF composition is normal but the opening CSF pressure is in most cases increased (>20cm $H_2O$ in normal weight patients and >25cm $H_2O$ in obese patients) [92]. Revised diagnostic criteria for IIH have been proposed by Friedman et al. including both clinical and neuroimaging findings [93]. Neuroimaging must precede diagnostic lumbar puncture to exclude increased CSF pressure due to other causes, including brain tumor, dural sinus thrombosis, infection, hydrocephalus.

Structural MRI is the cornerstone for IIH diagnosis, which enables the exclusion of other underlying causes of elevated intracranial pressure, but also facilitates the identification of neuroimaging abnormalities characteristic for IIH. The main axes of neuroimaging should be tailored to assess the orbits and the intracranial compartment. Orbital changes comprise (i) prominent subarachnoid space around the optic nerves with vertical tortuosity, (ii) flattening of the posterior sclera followed by intraocular protrusion, and (iii) enhancement of the optic nerve head [94-96]. The majority of imaging findings in the intracranial cavity are associated with the enlargement of outpouchings of the arachnoid space. The most suggestive imaging findings of IIH intracranially are the 'empty sella' sign, depicted as loss of the midsagittal height of the pituitary gland, and the Meckel's cave enlargement, depicted as enlargement

**Figure 11.** 32-year-old female patient, complaining for headaches, with confirmed by lumbar puncture Idiopathic Intracranial Hypertension, demonstrating in sagittal (A) and coronal T2W (B), as well as in transverse FLAIR (C) images the classic "empty sella" sign, and the optic nerves with vertical tortuosity. No signs of arterial or venous sinuses thrombosis in MRA (D) and MRV (E). Normal values in whole brain Volumetric analysis (F). The patient was treated with acetazolamide, as she refused the neurosurgical shunting procedure




of the porus trigeminus notch accompanied by a smooth cystic space in the anteromedial petrous apex [97, 98].Semiautomated volumetric methods can quantitatively assess the volume of the optic nerve sheath and pituitary gland. Objective metrics derived from the volumetric assessment may be utilized both for the diagnosis and follow-up of IIH patients [99].

Another suggestive imaging feature of IIH occurring in 65-90% of cases is transverse sinus narrowing depicted on MR venography, which may require further investigation with contrast-enhanced 3D MR venography or invasive digital subtracted venography [100]. Other less common signs of IIH are slit-like ventricles and acquired tonsillar ectopia, which is a mimicker of Chiari Malformation Type 1 [101]. Phase-contrast cine magnetic resonance imaging (PCC-MRI) and derived CSF parameters have also been used as a non-invasive technique for IIH diagnosis and treatment follow-up [102] (Figure 11).

*Chiari Malformation Type 1 (CM1)*

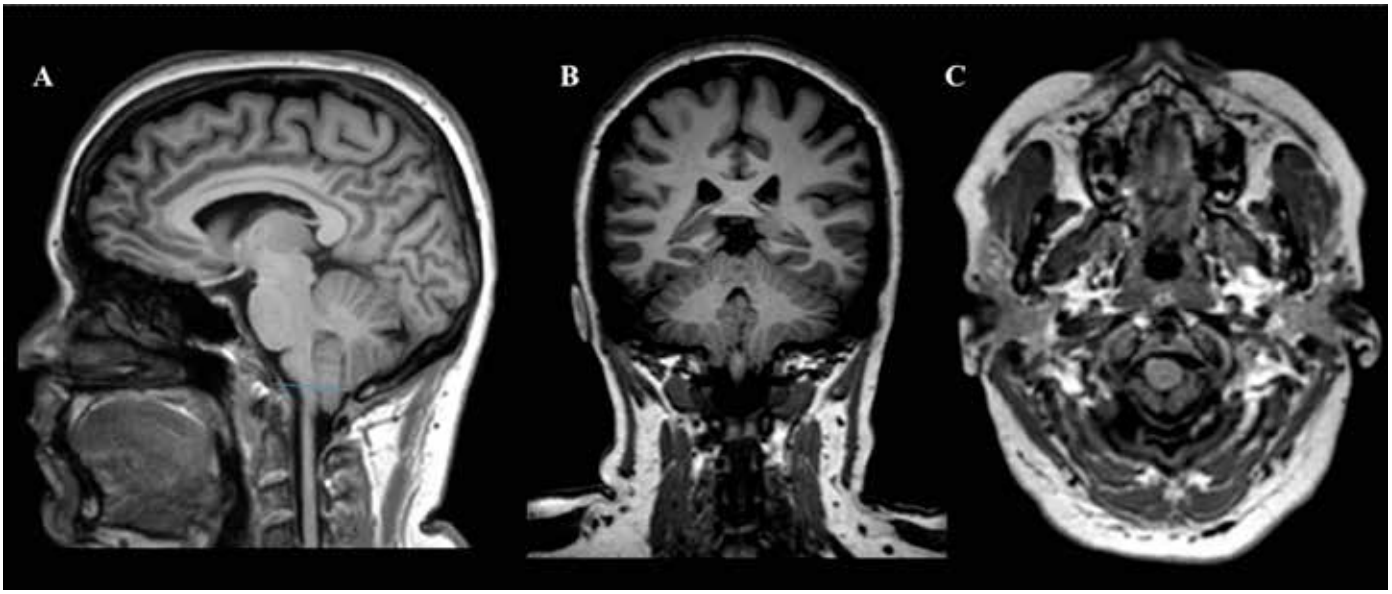
The hallmark of Chiari Malformation Type 1 is the projection and downward displacement of the cerebellar tonsils through the foramen magnum. The clinical features of CM1 are proportional to the degree of tonsillar prolapse. Headache is a common presenting symptom of CM1, along with symptoms associated with brainstem compression / dysfunction, syringomyelia, or hydrocephalus [103]. Furthermore, it should be mentioned that Valsalva maneuver or cough can provoke headache in the setting of CM1. Low-lying tonsils (benign tonsillar ectopia) must be differentiated from CM1, with the former being asymptomatic and considered an incidental finding compatible with tonsillar protrusion of up to 3-5 mm through the foramen magnum.

The imaging modality of choice for the diagnosis of CM1 is MRI. The cerebral tonsillar position can be accurately assessed on MRI and the degree of caudal descent can be measured, preferably on midsagittal plane. The imaging signs supporting CM1 include pointed tonsils referred as 'peg-like' tonsils, vertically oriented sulci referred as 'UK sergeant stripes' and crowding of subarachnoid space at the level of craniocervical junction by tonsillar prolapse mainly observed on axial images (Figure 12) [104]. Measuring of the CSF flow with PC-MRI may be abnormal in cases of CM1 due to pulsatile motion of tonsils [105]. The imaging protocol should include spinal cord MRI in order to exclude the presence of syringomyelia, that may be evident in 40% of patients with CM1 [106].

*Brain Tumour*

As already mentioned, headache can be caused by any space-occupying brain lesion. The headache pattern caused by brain neoplasms varies and the

**Figure 12.** Cerebral tonsillar caudal descent through the foramen magnum attributed to Chiari Malformation Type I. (A) On sagittal image, the cerebellar tonsils are low-lying (>5mm) and appear 'peg like' and pointed. Cerebellar tonsillar position is the vertical distance (purple line) from the tip of the cerebellar tonsils to a line drawn between the anterior and posterior rims of the foramen magnum, known as McRae line (blue line). (B) On coronal image, the tonsillar caudal descent is depicted. (C) Axial image through the foramen shows crowding of the medulla by the tonsils. No syrinx was evident




majority of patients presents with atypical findings [107]. Recently, advanced MRI techniques have radically changed the diagnostic approach to intracranial tumours. The WHO 2021 classification and grading of brain neoplasms has added more information about the phenotype of brain tumours and their genetic-molecular and genetic–prognostic correlations [108]. Conventional and advanced MRI techniques enable the diagnosis and staging of brain tumours, neurosurgical and radiotherapy planning, as well as treatment monitoring differentiating between pseudoprogression, progression or recurrence (Figures 13-16) [109].

## Secondary headache attributed to infection

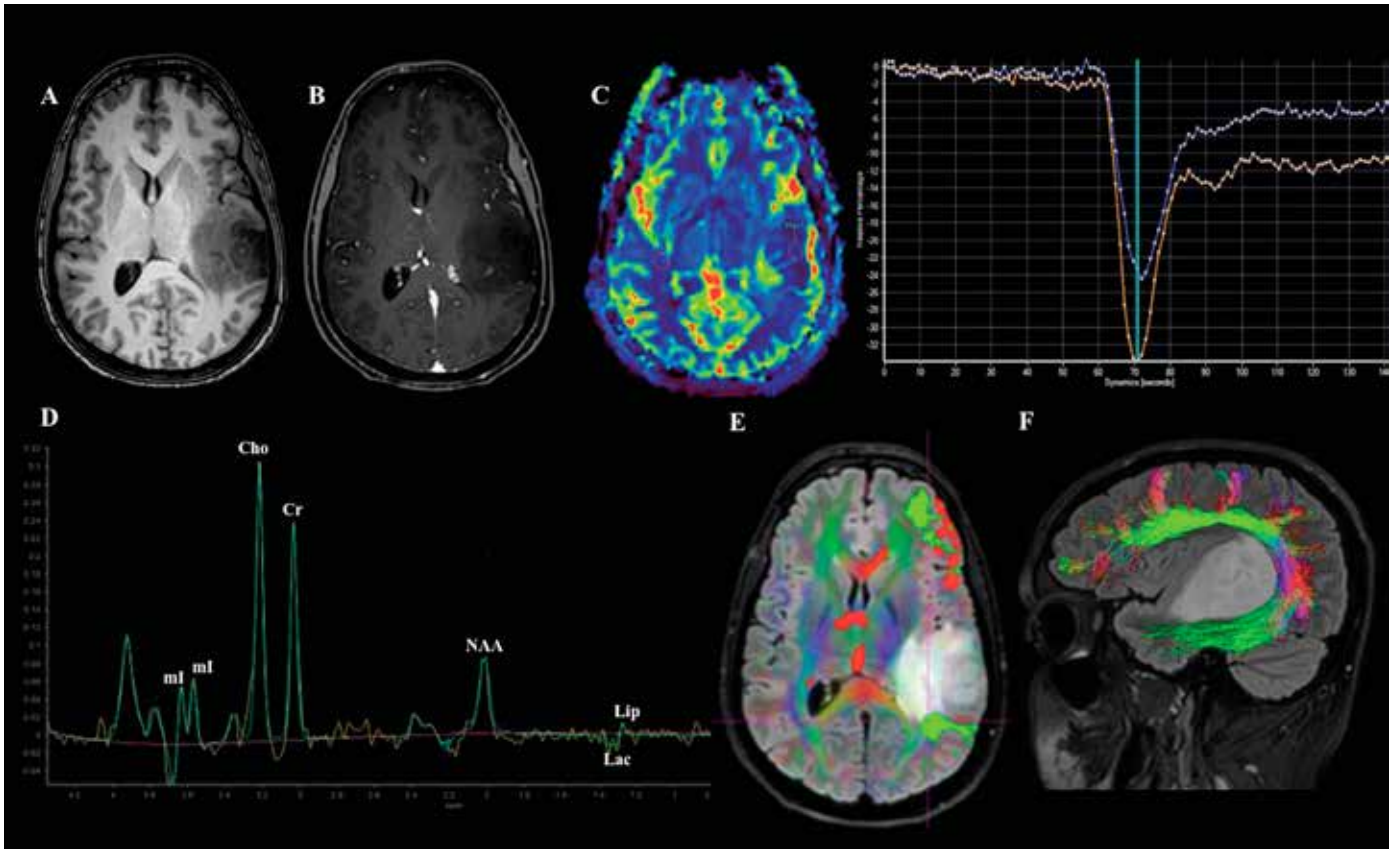
*Brain Abscess*

A cerebral abscess is a consequence of encephalitis and is typically characterized by accumulation of pus, which is surrounded by a capsule. Encephalitis and brain abscess can result from haematogenous dissemination (i.e., endocarditis), or as a complication of contiguous spread from paranasal sinuses, odontogenic or ear infection. Headache may be present in 69% of patients, but only 20% of them will suffer from the classic triad, which consists of headache, fever and focal neurologic deficits [110].

The pathogenesis of a brain abscess includes four distinct stages: early cerebritis (1-3 days), late cerebritis (4-9 days), early capsule formation (10-13 days) and late capsule formation (from 14 days onwards). Furthermore, five histological zones have been described, that can aid understanding of the neuroimaging findings: (1) a necrotic centre; (2) an external zone of accumulated inflammatory cells, macrophages and fibroblasts; (3) a capsule with dense collagen; and (4) peripheral astrogliosis and edema [111].

With respect to neuroimaging, CT scan is not as sensitive as MR, with 6% of cases having false negative CT-findings. CT scan is invaluable in the ER for assessment of the degree of brain edema [111]. Besides abscess diagnosis, both CT and MRI may be used to depict potential complications, including ventriculitis and CSF obstruction with secondary hydrocephalus. With respect to MRI studies, conventional MRI sequences can be combined with complementary advanced MRI techniques (MR spectroscopy) for obtaining information that may be suggestive of specific pathogens. The necrotic centre of an abscess will appear on MRI with high signal on T2W, a three-layered low-signal capsule on T2W and vivid capsule enhancement on T1W after gadolinium injection [112]. Beyond conventional imaging, the abscess cavity is depicted with high signal on DWI with corresponding low value on ADC map, due to the purulent content. Furthermore, MR-perfusion helps in differentiating a brain abscess with low regional cerebral blood volume (rCBV) from a brain tumor with necrotic part, which typically has high rCBV due to high vascularization. Despite the use of advanced imaging, however, diagnostic difficulties in differentiating between abscess and brain tumour

**Figure 13.** A 32-year-old male presented with headache and on MRI a space occupying lesion is depicted, mainly located on the left temporal lobe. On T1W image (A), the lesion shows inhomogeneous low signal with no evident enhancement on post contrast T1W (B). (C) On perfusion dynamic susceptibility contrast T2* (DSC-T2*) the relative cerebral blood volume (rCBV) ration was calculated 3.79, compatible with high grade brain tumor. (D) On TE=144ms single voxel MRS inside the lesion, increased concentrations of choline (Cho), creatine (Cr), lactate (Lac) and lipids (Lip) are depicted with Cho / Cr ratio of 1.35 and Cho / NAA 2.38. Furthermore, peaks of myoinositol (mI) are depicted, a finding that supports the differentiation of a lower-grade glioma into a higher-grade glioma. (E) Presurgical task-based functional MRI (TB-fMRI) and Resting-State fMRI (RS-fMRI) based on the Blood oxygenation level dependent (BOLD) phenomenon were acquired and the lateralization of hippocampal and language networks was left-sided. The lesion was in close proximity, distance <1cm, with the posterior part of the left upper temporal gyrus (Wernicke), but also with the primary auditory cortex. The distance of the lesion from the Broca's area (inferior frontal gyrus) was clearly bigger than 2cm. (E) On Diffusion tensor imaging tractography –DTI tractography– the lesion was in close proximity with, probably infiltrating, the posterior part of the left superior longitudinal (arcuate) fasciculus, the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus




may arise in the early stages of capsule formation, when increased capillary density of the abscess may correspond to increased rCBV and lead to misdiagnosis [111].

MR Spectroscopy (MRS) is another advanced method widely performed for differential diagnosis of brain lesions that enables the delineation of their metabolic profile. MRS may show peaks of amino acids, lactate, lipids, succinate, acetate and alanine. The presence of peaks of amino acids is a sensitive marker of pyogenic abscess due to the breakdown of neutrophils inside the capsule, releasing proteolytic enzymes, which hydrolyse proteins into amino acids. However, absence of amino acids on MRS may be noted in patients with brain abscess who have undergone previous treatment with antibiotics. Furthermore, the peak of acetate with or without succinate on MRS has been described as a signature feature for anaerobic infection (Figures 17, 18) [113].

## Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structures

*Rhinosinusitis*

Rhinosinusitis can be divided in acute, subacute

**Figure 14.** Presurgical mapping in a 54-year-old patient presented with headache and neurological deficits. (A) Task-based functional MRI (TB-fMRI) with a paradigm of tongue movement revealed close proximity of the space occupying lesion and the corresponding cortical activation area of the tongue motion. (B) Inferior frontal gyrus (Broca's area) and superior temporal gyrus (Wernicke's area) activations in TB fMRI showed left-side lateralization of language. (C) Diffusion tensor imaging tractography depicted signs of probable infiltration of the right corticospinal tract and the right superior longitudinal fasciculus

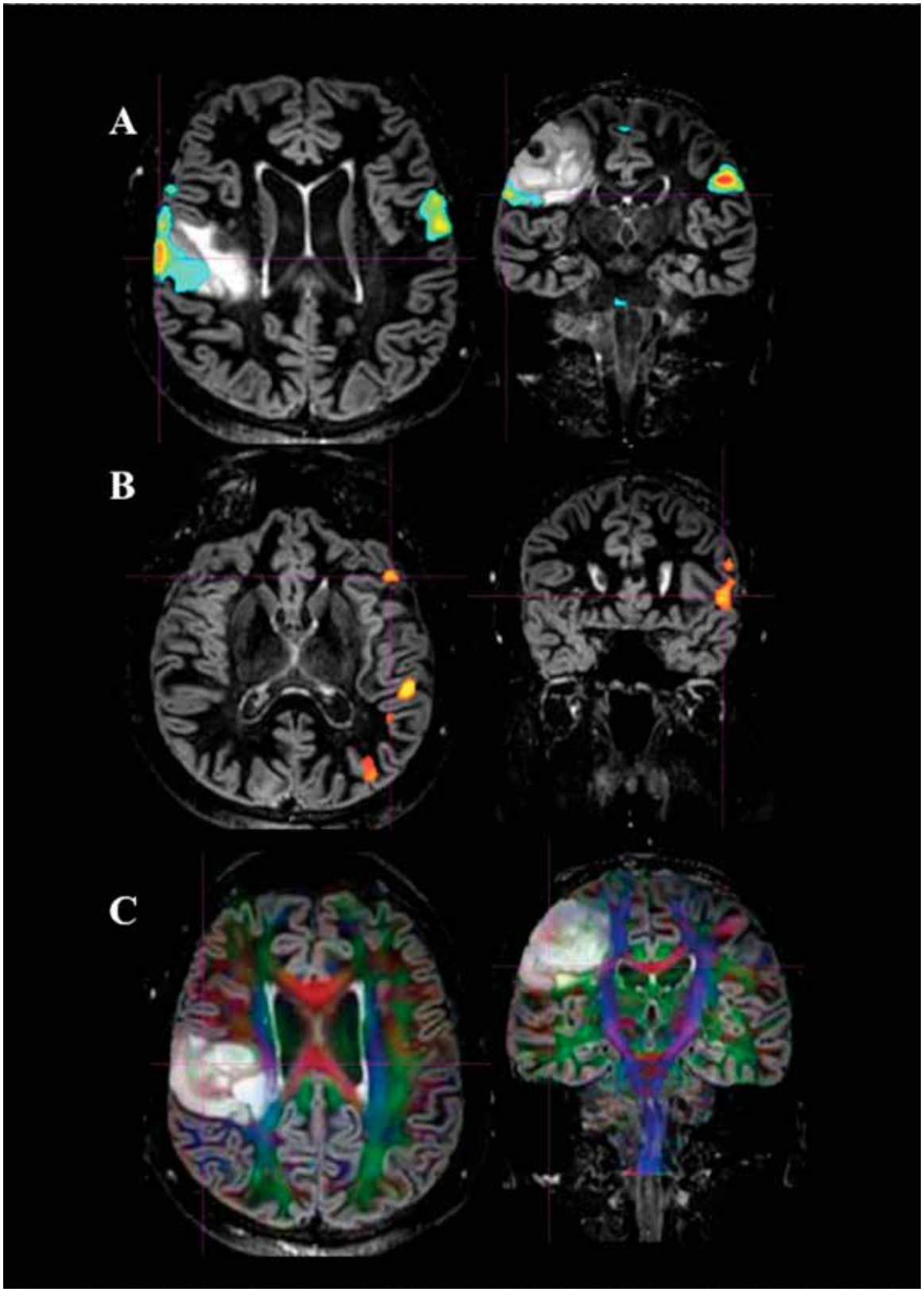
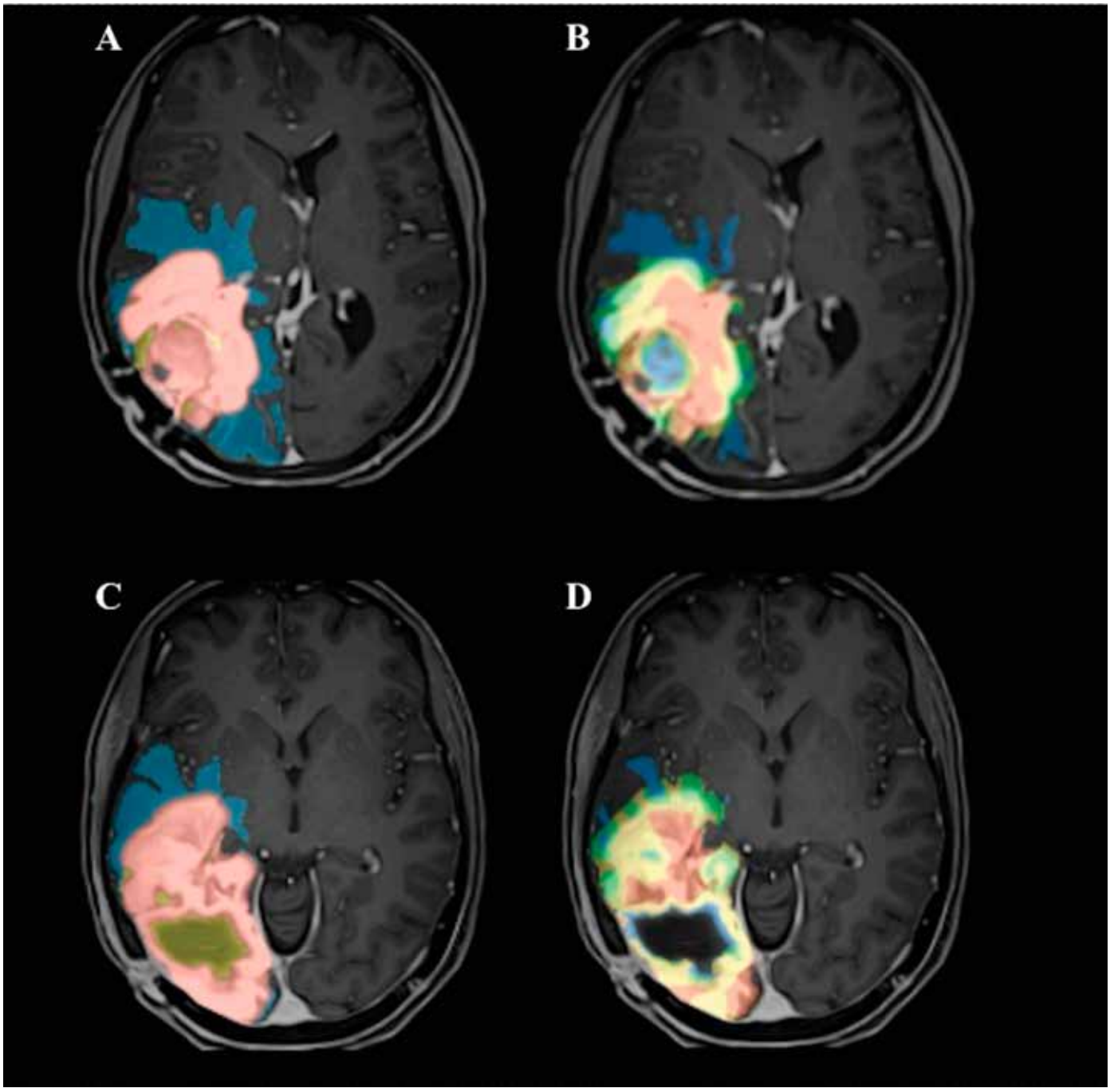
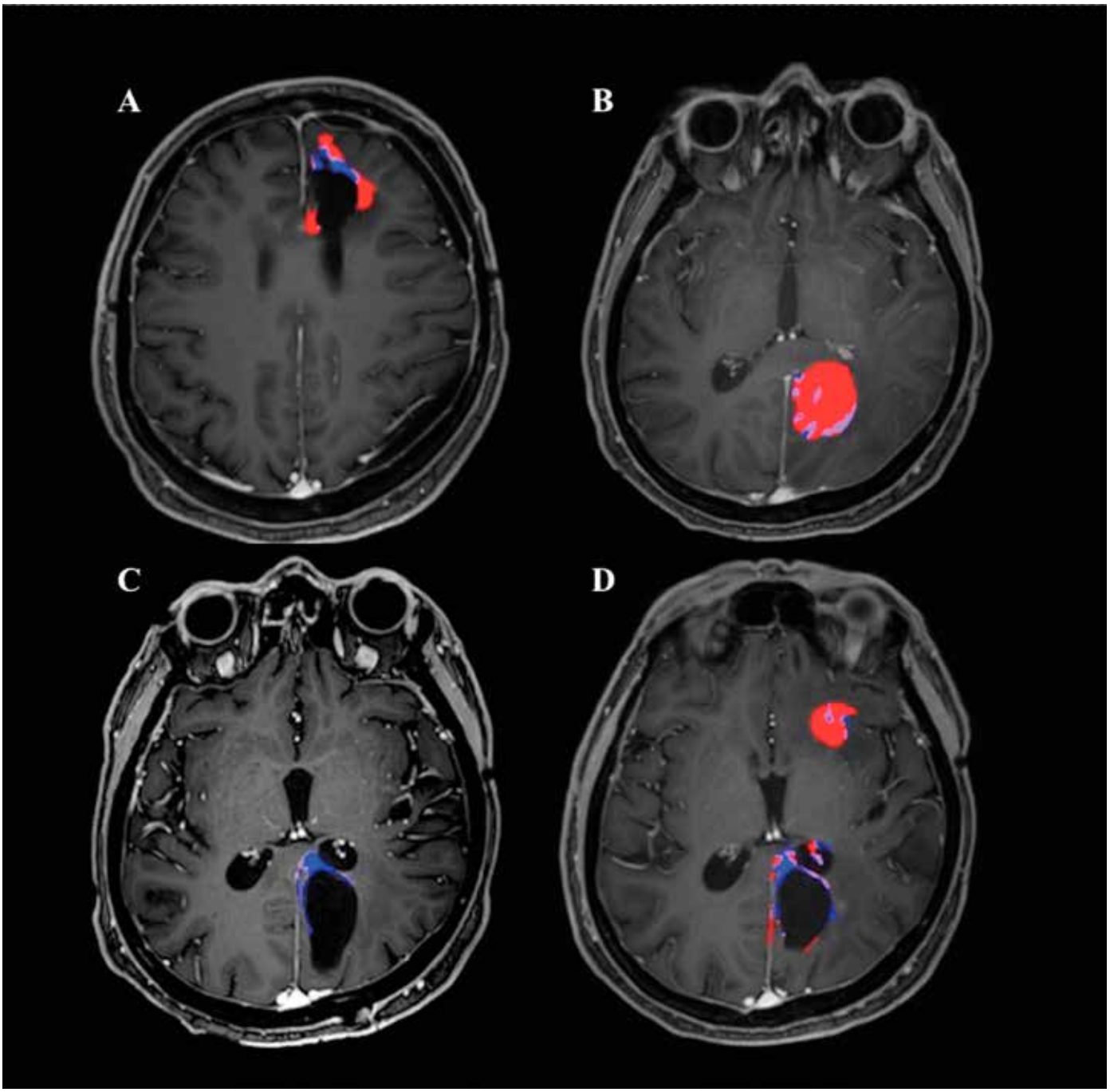


**Figure 15.** Artificial Intelligence (AI) segmentation for presurgical mapping and follow-up. (A) Presurgical AI anatomical segmentation map and volumetric assessment of enhancing tumor (pink-93.70ml), edema (blue-135.52ml) and necrosis (green-8ml) (B) Presurgical AI quantification based on perfusion dynamic susceptibility contrast T2* (DSC-T2*), for the description of vascular heterogeneity of the enhancing tumor and edema tissues in terms of the angiogenic process located at these regions. Red colour depicts high angiogenic enhancing tumor region-HAT (30.7ml), yellow colour depicts low angiogenic enhancing tumor region-LAT (45.55ml), green colour depicts potentially tumor infiltrated peripheral edema–IPE (28.86ml) and blue colour depicts pure vasogenic edema-VPE (82.75ml). (C) Post-surgery follow-up with AI segmentation maps and volumetric metrics (enhancing tumor-94.47ml, edema-133.21ml and necrosis-18ml). (D) Post-surgery follow-up AI with based on DSC-T2* quantification (HAT-22.88ml, LAT-54.04ml, IPE-25.61ml, VPE-83.44ml)



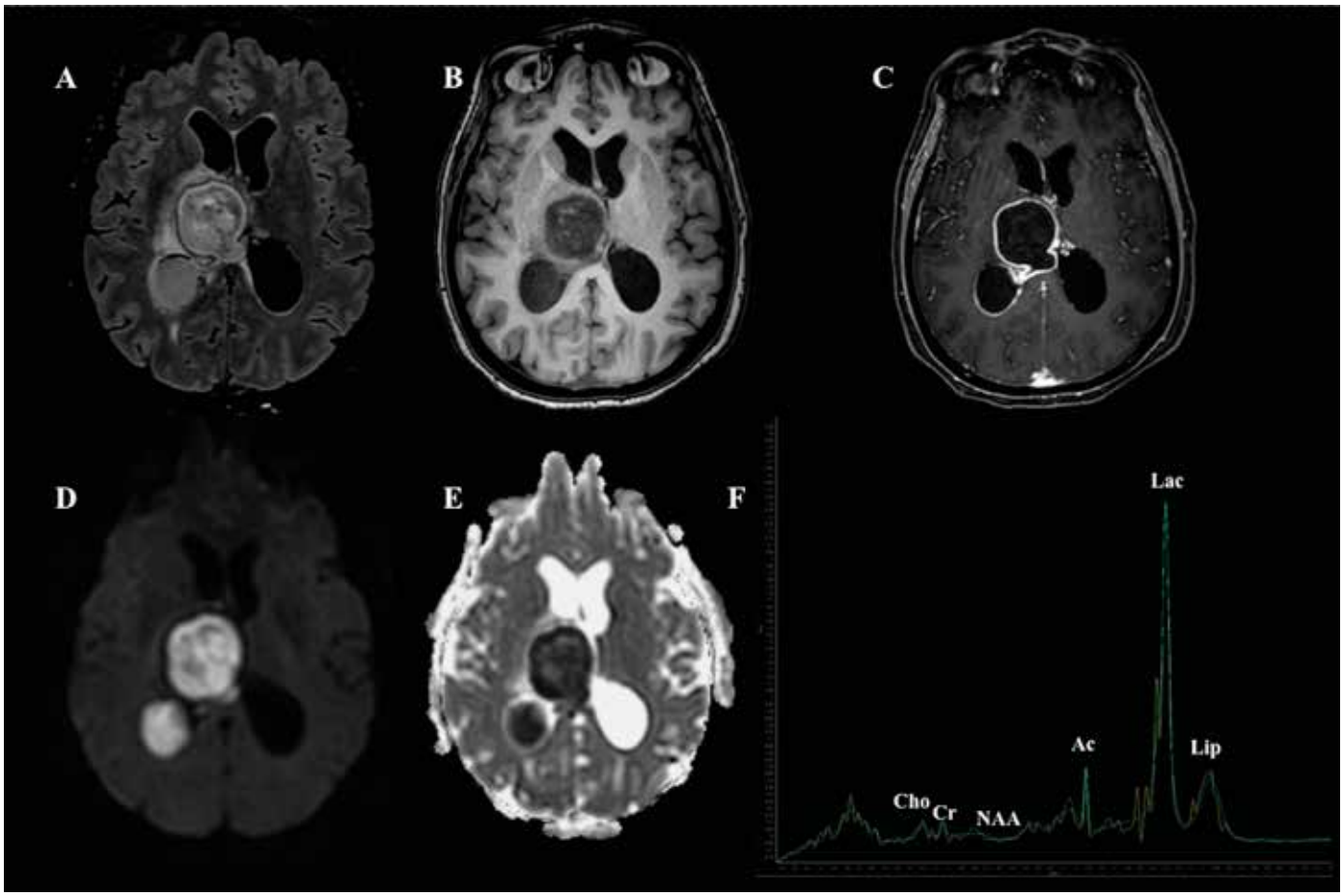

and chronic depending on the duration of symptoms. Headache is the most frequent clinical symptom of rhinosinusitis. With respect to neuroimaging, imaging findings of rhinosinusitis are non-specific and must always be correlated with evidence from clinical and/or endoscopic exams. It is noteworthy that 20-40%

**Figure 16.** DSC – T2* Perfusion MRI - based Fractional Tumor Burden (FTB) in the follow up of a glioblastoma multiforme patient with prior surgery and radio-chemo-therapy (red colour-rCBV>1.556 representing areas of high relative cerebral blood volume (rCBV), purple colour- 1<rCBV<1.556 representing areas with mild increased rCBV, blue colour - rCBV<1 representing normal rCBV). (A) Signs of relapse were evident (red colour-58.8%). (B) On the left frontal lobe, no signs of residual tumor were evident after the second surgery, but a new lesion on the left occipital lobe was depicted. This lesion consisted with 74.7% with rCBV>1.556, 20.8% with 1<rCBV<1.556 and 4.4% with rCBV<1. (C) Follow-up MRI after the third surgery did not reveal signs of residual tumor or relapse. (D) On follow-up MRI post-radiotherapy and post-chemotherapy, a new lesion on the left temporal lobe was depicted with 58.9% of rCBV>1.556




of patients undergoing MRI for any indication may incidentally show imaging abnormalities suggestive of rhinosinusitis [114]. Plain radiographs are part of the initial work up but have some limitations in assessing the extent of the inflammation, the sphenoid sinuses and potential complications of rhinosinusitis. CT scan remains the imaging modality of choice for depicting sinonasal cavities with higher anatomical

**Figure 17.** A female, who underwent dental surgery complained for headache and fever. On axial FLAIR (A), a high-signal-intensity mass with a low-signal-intensity capsule was detected. Perilesional high-signal-intensity vasogenic edema was also noted. Furthermore, high-signal –intensity was also revealed inside the right lateral ventricle. On axial T1W image (B) the lesion showed low-signal-intensity and the right lateral ventricle showed intermediate/high-signal intensity. On T1W post contrast (C) ring-like enhancement of the lesion was detected, as well as contrast enhancement was noted on the wall of the right lateral ventricle. On DWI b=1000 (D) the centre of the lesion showed a high signal, as well as inside the right lateral ventricle, with low ADC values (E), reflecting diffusion restriction. On TE=144ms single voxel MR-Spectroscopy (F) peaks of lipids (Lip), lactate (Lac), amino acids and **acetate (Ac)** were evident. All the imaging findings were compatible with pyogenic abscess complicated with ventriculitis. Staphylococcus epidermis was shown as the pathogenic microorganism after surgical aspiration of the lesion



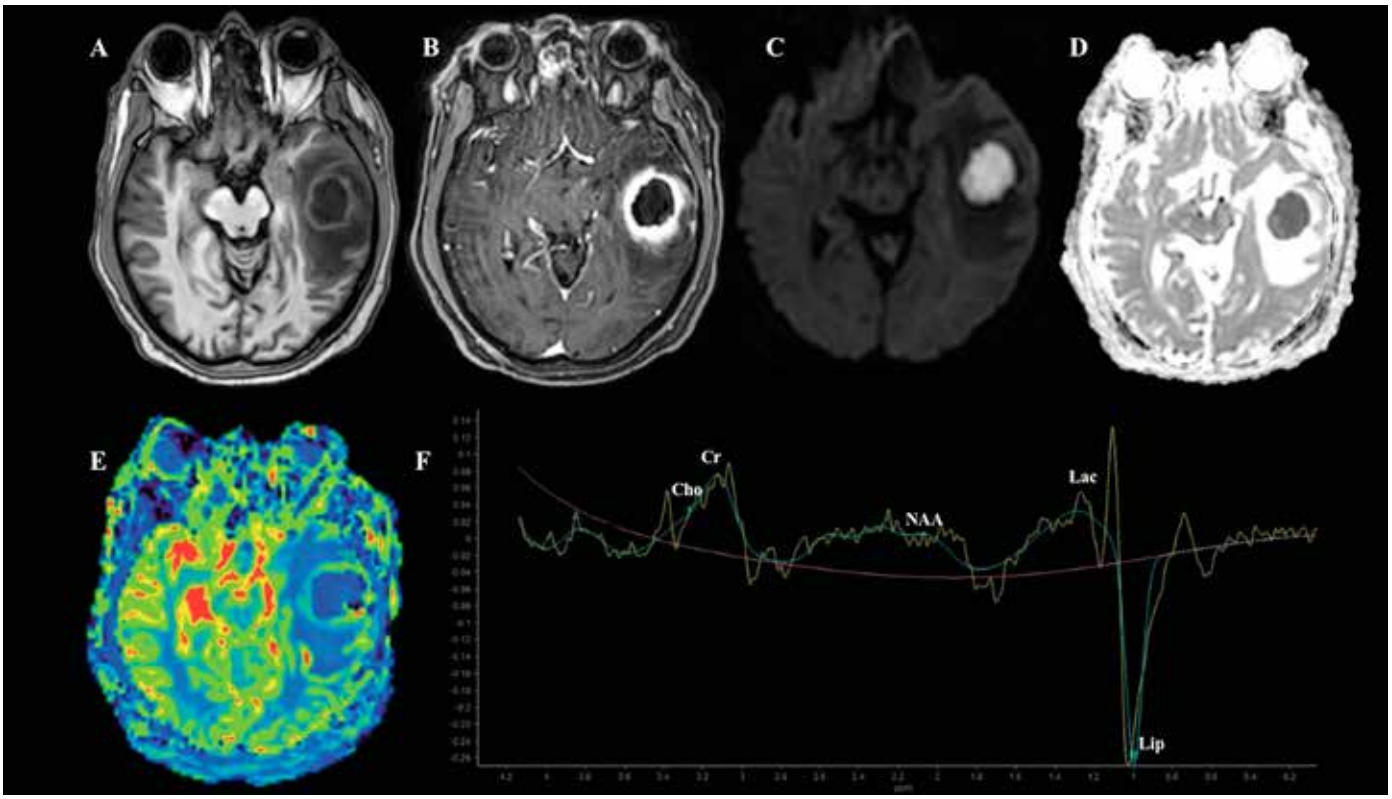

accuracy and can also be used as preoperative evaluation method [115]. Furthermore, CT scan is preferred for bone assessment, especially when chronic sinusitis is suspected. On the other hand, MRI has been suggested as the preferred imaging modality for evaluation of intracranial and orbital complications. Additionally, MRI is superior to CT for differentiating between inflammatory and neoplastic processes, while in case of a neoplasm MRI can also facilitate staging and surgery planning [116, 117].

Mucosal thickening along with presence of gas-fluid level and air bubbles within the paranasal sinuses are prominent on CT in acute rhinosinusitis, while when fungal infection is suspected, CT may reveal hyperdense lesions and probable calcifications within the paranasal sinuses [116, 118]. On T1 weighted images the mucosal thickening is isointense to soft tissue and the fluid is hypointense. On T2 weighted images both mucosal thickening and fluid will be hyperintense. On post contrast T1 weighted image only the inflamed mucosa will enhance in cases of acute rhinosinusitis or when acute and chronic rhinosinusitis concur (Figure 19). Bone sclerosis, rarefaction and periosteal reaction are best evaluated on CT scan and are considered hallmarks of chronic rhinosinusitis [116, 118].

*Trigeminal Neuralgia (TN)*

Trigeminal neuralgia (TN) belongs to the neuropathic facial pain syndromes and is defined according

**Figure 18.** A 66-year-old male patient with previous history of odontogenic infection presented with headache and neurological deficits along with fever and confusion. On MRI a space- occupying lesion on the left temporal lobe was detected. On T1W (A), the lesion showed inhomogeneous low signal with ring enhancement on post-contrast T1W (B). The central part of the lesion showed diffusion restriction with high signal on DWI b=1000(C) and low-signal on ADC map (D). On perfusion DSC T2* (H) the relative cerebral blood volume (rCBV) ratio was lower than 1.75. On intermediate TE=144ms single voxel MR-Spectroscopy (F) peaks of lipids (Lip), lactate (Lac), amino acids and *especially* acetate were evident. All the imaging findings and the patient history were suggestive of brain abscess, confirmed by surgical excision




to the ICHD-III as unilateral distribution of a brief electric shock-like pain, limited to the distribution of one or more divisions of the trigeminal nerve [2, 119]. TN most frequently affects the maxillary or mandibular division of the trigeminal nerve. An innocuous stimulus may trigger the nerve abruptly. According to a recently proposed classification system, TN of unknown aetiology is categorized as idiopathic; TN caused by neurovascular compression is labelled as Classical TN; and TN associated with structural abnormalities (i.e., demyelinating lesions and neoplasms) is characterized as secondary TN [120].

- Classical TN

Classical TN is caused by a vascular loop, most commonly arterial, either deriving from the superior cerebellar artery or its branches, compressing the cisternal portion of the trigeminal nerve. Less commonly the vascular loop is formed by the transverse pontine vein, which compresses the trigeminal nerve [121]. The development of high-resolution 3D MRI sequences has increased the diagnostic sensitivity of vascular loop identification which may enable selection of patients that may benefit from microvascular decompressive surgery. Of note, that imaging findings suggestive of indentation of the trigeminal nerve by a vascular loop may be incidentalomas in patients undergoing MRI, but are far more common in symptomatic TN patients [122, 123]. GRE sequences and contrast-enhanced MRA can reveal the neurovascular contact at the root entry or exit zone of the trigeminal nerve on the affected side (Figure 20) [124]. Furthermore, some studies suggest that fractional anisotropy (FA) on diffusion-tensor imaging (DTI) is significantly lower at the affected side compared to the contralateral side [125, 126].

- TN secondary to Multiple Sclerosis (MS)

Patients with MS suffer from different types of neuropathic pain, among which TN is highly predominant. The prevalence of TN in patients with MS ranges from 1.4% to 4.9% [127] and the diagnosis of TN may precede the diagnosis of MS in some cases [128].

**Figure 19.** (A) On axial T1W, peripheral mucosal thickening in maxillary sinuses and ethmoidal cells is depicted along with the presence of fluid-air level and strong enhancement on post-contrast T1W (B), imaging finding suggestive of acute rhinosinusitis

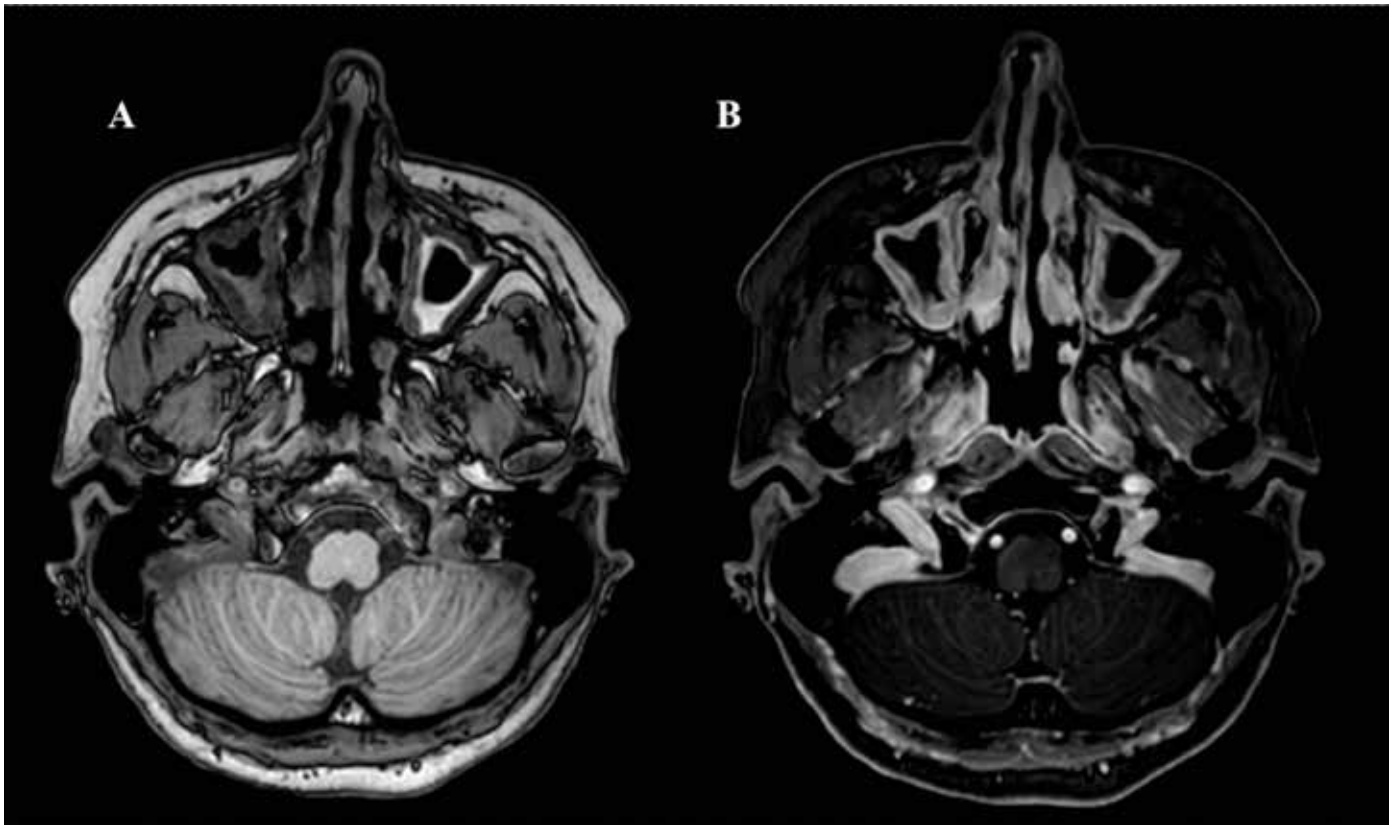
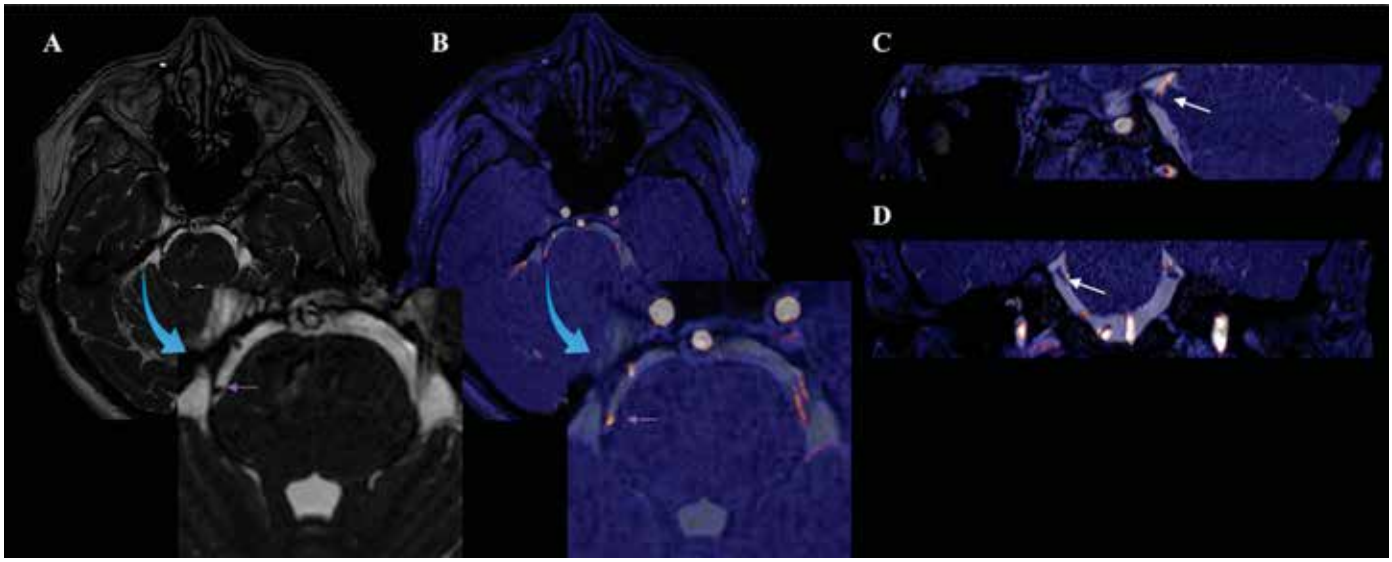


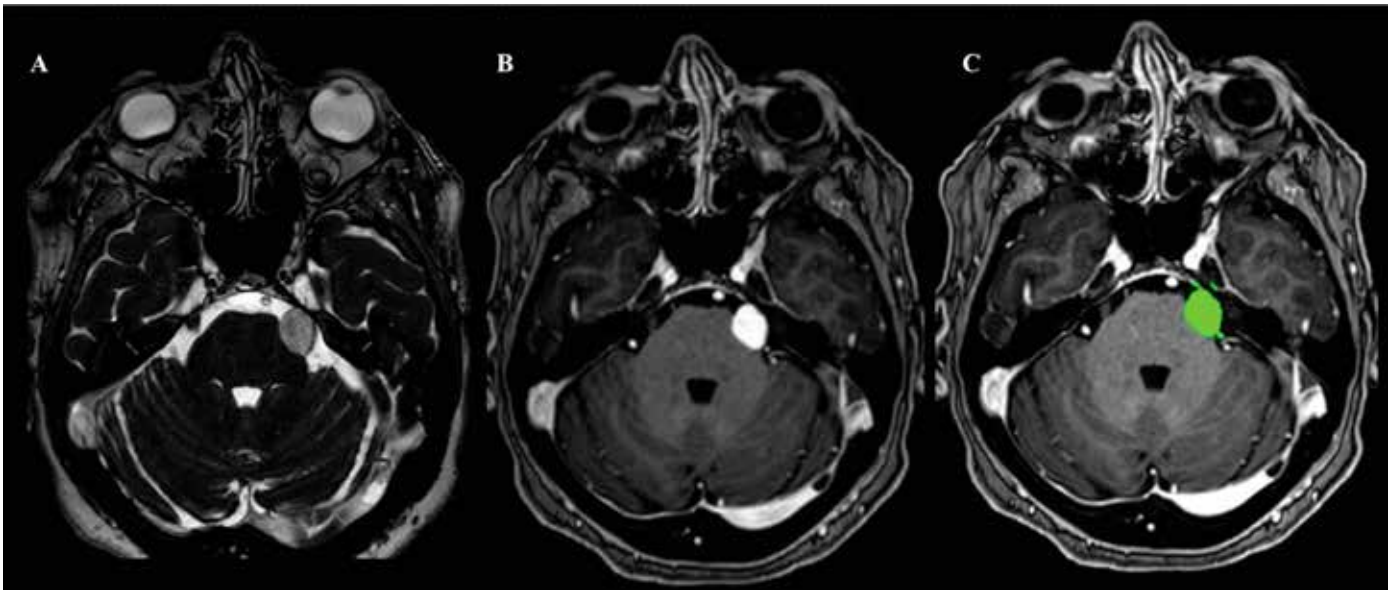

**Figure 20.** Right neurovascular compression by an arterial loop derived from the right superior cerebellar artery indenting the ipsilateral trigeminal nerve at its inferior surface with associated trigeminal nerve atrophy, depicted on heavily T2 weighted high-resolution axial image (A) and on MRA (B-axial, C-sagittal, D-coronal)




It has been established that TN secondary to MS is associated with the presence of a linear pontine demyelinating plaque involving the intrapontine segment of the trigeminal nerve, specifically in the area between the root entry zone and the nuclei [129].

The diagnosis of TN in patients with MS is based

**Figure 21.** A well-defined extra axial mass of the left trigeminal nerve is depicted at the left cerebellopontine angle cistern posteriorly to Meckel's cave. Balanced fast field-echo (BFFE) sequence provides detailed anatomical relationship between the mass and the left trigeminal nerve (A). On post-contrast T1 weighted image the lesion shows enhancement (B) with an estimated volume of 1.7441ml (C)




on neurophysiological techniques and MRI for the identification of trigeminal pathway impairment [120]. As MRI is routinely used for the diagnosis and follow-up of MS, a standardized MRI protocol has been suggested [130]. Therefore, in a patient with MS suffering from TN, besides MRI findings compatible with MS, a pontine lesion will be evident. This lesion will be more frequently unilateral, localized in the ventrolateral pons between the trigeminal root entry zone and the trigeminal nuclei, affecting the intrapontine part of primary afferents of the trigeminal nerve (Figure 21) [131].

- TN secondary to schwannoma

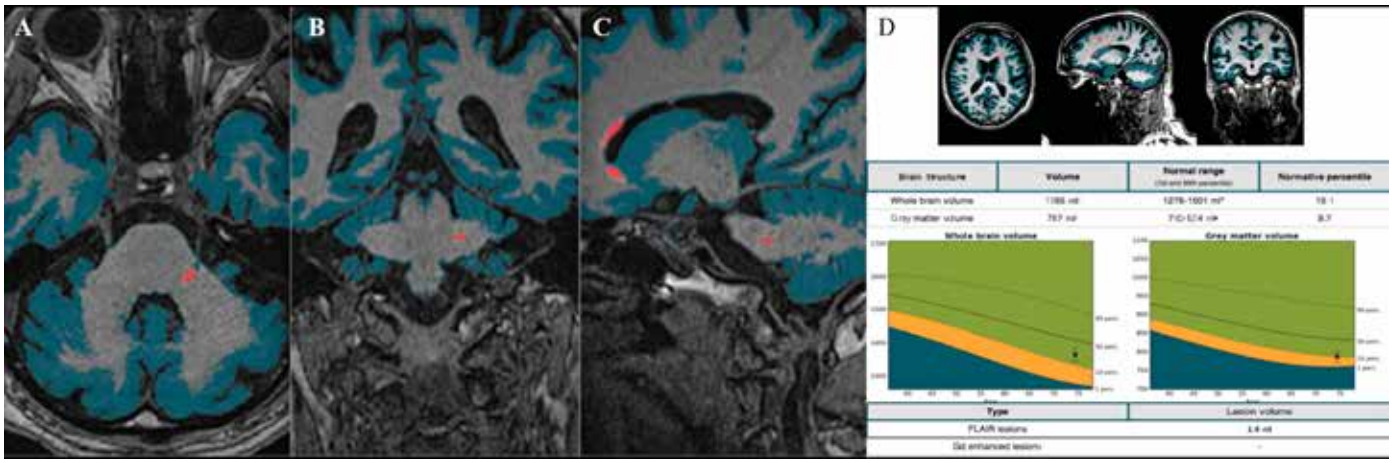
Trigeminal schwannoma is the second most common schwannoma following the vestibular schwannoma, mainly occurring in middle-aged adults, with a slight female preponderance. Trigeminal schwannomas are either sporadic or associated with neurofibromatosis type 2 (NF2). This type of schwannoma originates from nerve-sheath Schwann cells, therefore appears as a mass with well-defined margins abutting the nerve. If the schwannoma is confined in one compartment of the nerve it is subcategorized either as preganglionic (cisternal), ganglionic (confined to Meckel's cave) or postganglionic [132]. MRI establishes the location of the schwannoma, the approximate volume and its proximity to important anatomical structures, especially when surgical treatment is indicated. Imaging findings depend on the schwannoma size. Small schwannomas appear homogenously iso- or hypointense on T1- and T2-weighted images with avid enhancement after intravenous gadolinium administration. However, when they become larger, they show heterogeneous signal due to intratumoral necrosis or haemorrhage. Magnetic Resonance Cisternography is important for the proper assessment of the cisternal segment of the trigeminal nerve (Figure 22). CT scan is complementary to MRI in cases of bone erosions i.e., petrous apex erosion [133].

Quantitative MRI Volumetry and Dynamic Contrast-Enhanced (DCE) perfusion may be indicated for follow-up of trigeminal schwannoma after gamma knife stereotactic radiosurgery [134].

## Conclusion

Headache is one of the most common clinical manifestations of neurological patients. Thorough neurological examination, recognition of red flags and worrisome features, as well as detailed patient history-taking help the clinician classify headache as primary or secondary, according to the ICDH-III. The optimal neuroimaging methods and protocols for headache diagnosis should be decided on an individual patient basis depending on the clinical suspicion of underlying headache causes. Overall, MRI is preferred for the delineation of underlying brain pathology in patients presenting with headache, with the exception of subarachnoid haemorrhage that necessitates performance of CT in the acute setting, as CT is characterized by higher sensitivity compared

**Figure 22.** A 74-years-old male with trigeminal neuralgia secondary to MS. On the axial (A), coronal (B) and sagittal (C) plane a pontine lesion in the left intrapontine fascicular part of the trigeminal nerve is noted (red colour) corresponding to a linear demyelinating plaque with associated trigeminal nerve atrophy. Images (A), (B) and (C) are derived after whole brain volumetric analysis using artificial intelligence and segmentation of grey, white matter, CSF and lesions. (D) Whole brain quantitative volumetry did not indicate brain atrophy, since the volume of the whole brain and grey matter are within the normal range for the age and sex of the examinee, while 1.4ml lesion load on FLAIR images were calculated with no enhancing lesion




to MRI in the acute phase for detecting subarachnoid haemorrhage. In conclusion, conventional and advanced MRI techniques provide invaluable information regarding the underlying aetiology of secondary headaches and comprise indispensable tools in clinical practice for treatment planning and follow-up of patients suffering from secondary headache.

## Conflicts of Interest Statement

The authors declare no conflicts of interest

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# Βιβλιοπαρουσιάσεις

κυκλοφόρησαν και σας ενημερώνουμε

# Ημικρανία & άλλες κεφαλαλγίες

*Δρ. Μιχάλης Βικελής και συν.*

## Βιβλιοκριτική παρουσίαση

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# Migraine and other headaches

*Michalis Vikelis et al.*

## A book review

*by George Georgiadis*


Πριν από μερικές μέρες έγινα κάτοχος του βιβλίου «Ημικρανία και άλλες κεφαλαλγίες» του συγγραφέα Μ. Βικελή & συν. έκδοση του Συλλόγου Ασθενών με ημικρανία & Κεφαλαλγία Ελλάδος.

Αρχικά εντυπωσιάστηκα από την εξαιρετικά καλαίσθητη έκδοση & έτσι ενισχύθηκε η άποψη μου ότι πιάνοντας στα χέρια σου ένα καλό βιβλίο λυπάσαι για τις ώρες που χάνονται μπροστά στις ψυχρές οθόνες και για το ότι, σύμφωνα με διεθνείς στατιστικές, οι Έλληνες υστερούν στην αγορά & μελέτη βιβλίων.

Θα μπορούσε κανείς να αναρωτηθεί για τη σκοπιμότητα μιας ακόμα έκδοσης με θέμα τις κεφαλαλγίες και ειδικότερα την ημικρανία. Τα τελευταία όμως χρόνια σημαντικό μέρος της ιατρικής γνώσης στράφηκε σε νοσήματα που, αν και δε σκοτώνουν, αποτελούν σημαντικές αιτίες πρόκλησης μειωμένης ικανότητας για λειτουργικότητα δηλαδή επηρεάζουν αρνητικά την ποιότητα ζωής των πασχόντων. Μεταξύ αυτών η ημικρανία κατέχει μια σημαντική θέση στην πρώτη δεκάδα αλλά εξακολουθεί να παραμένει υποτι-

μημένη πάθηση και μάλιστα είναι ευρέως διαδεδομένη –αλλά λαθεμένη– η άποψη πως η ημικρανία δε μπορεί να θεραπευθεί.

Έτσι, το ενδιαφερόμενο αναγνωστικό κοινό, βρίσκει μια αξιόπιστη πηγή ενημέρωσης και ένα σημείο αναφοράς για τη μελέτη των κεφαλαλγιών που το βοηθάει να απομακρυνθεί από ατεκμηρίωτες, αβάσιμες μεθόδους θεραπείας.

Το βιβλίο αυτό, με απλά και κατανοητά λόγια, περιγράφει τα είδη των κεφαλαλγιών, προσφέρει χρήσιμες γνώσεις για την κατανόηση & αντιμετώπιση τους χωρίς όμως να χάνει την επιστημονική του εγκυρότητα.

Ο συγγραφέας, Δρ Μιχάλης Βικελής νευρολόγος, ιδιαίτερα εξειδικευμένος στις κεφαλαλγίες είναι γνωστός στην επιστημονική κοινότητα, διαθέτει ένα πλούσιο συγγραφικό έργο και μεγάλη εμπειρία στο θέμα αυτό. Κατάφερε, συνεπικουρούμενος από τον επιστημονικό σύμβουλο του συλλόγου ασθενών με κεφαλαλγία νευρολόγο Δρ Μανώλη Δερμιτζάκη, να συντονίσει σαν έμπειρος μαέστρος μια εκλεκτή ομάδα επιστημόνων που διαθέτουν όλοι πλούσια εμπειρία & έγραψε καθένας ειδικότερα κεφάλαια και έτσι το παρόν πόνημα να αποτελέσει ένα ιδιαίτερο ομαδικό έργο με τον κ. Βικελή να αποτελεί τον βασικό συγγραφέα.

Στα επί μέρους κεφάλαια του βιβλίου θα σταθώ στη προτροπή του συγγραφέα προς τους πάσχοντες να συμμετέχουν στη θεραπευτική διεργασία με τη πιστή τήρηση ημερολογίου της κεφαλαλγίας και στην προφύλαξη τους αποφεύγοντας τους πυροδοτικούς-εκλυτικούς παράγοντες. Ιδιαίτερη μνεία γίνεται στη διατροφή, στους γενετικούς και ορμονικούς μηχανισμούς, στην ιδιαίτερη επιβάρυνση των γυναικών και φυσικά στη συμπτωματολογία της ημικρανίας αλλά και των υπολοίπων κεφαλαλγιών προσθέτοντας σημαντική γνώση στον κάθε ενδιαφερόμενο. Το κεφάλαιο που αναφέρεται στην εργαστηριακή προσέγγιση θεωρώ ότι είναι ιδιαίτερα χρήσιμο και βοηθά τους ασθενείς να αποφεύγουν τις πολλές, συχνά κοστοβόρες και ενίοτε με βαθμό επικινδυνότητας, εξετάσεις.

Το τμήμα του βιβλίου που αναφέρεται στη θεραπεία είναι από τα πλέον ενδιαφέροντα & χρήσιμα. Η συζήτηση περιστρέφεται γύρω από όλες τις διαθέσιμες θεραπείες, παλαιότερες και πρόσφατες, πχ μονοκλωνικά αντισώματα, μη λησμονώντας τις εναλλακτικές θεραπείες, τα συμπληρώματα διατροφής αλλά και επεμβατικές (αλλαντική τοξίνη) και ¨χειρουργικές¨ θεραπείες τοποθετώντας αυτές στη πραγματική τους διάσταση.

Διάβασα επίσης με ενδιαφέρον τα τμήματα του βιβλίου που αφορούν τη γυναίκα (εγκυμοσύνη, αντισυλληπτικά χάπια) αλλά και το παιδί και στους ηλικιωμένους καθώς και την πορεία της ημικρανίας στο χρόνο.

Στο βιβλίο δεν παραλείπεται να αναφερθούν, όχι με κουραστικές λεπτομέρειες, και άλλες κεφαλαλγίες (αθροιστική, τάσεως κ.λπ.) διάφορες δευτεροπαθείς κεφαλαλγίες ( που κυρίως ανησυχούν, φοβίζουν τους ασθενείς) αλλά και διάφορες άλλες νευραλγίες της κεφαλής σπάνιες ή μη, ίσως με κάπως εκτενέστερη αναφορά στο ανεύρυσμα εγκεφάλου. Η αναφορά στο περίφημο ¨αυχενικό σύνδρομο ¨αλλά και στη μυθολογία που το περιβάλλει με βρίσκει απόλυτα σύμφωνο. Θα περίμενα μόνο μια κάπως πιο εκτεταμένη αναφορά στην κεφαλαλγία τάσεως λόγω της μεγάλης συχνότητας εμφάνισης της στον γενικό πληθυσμό και ίσως ένα μικρό ξεχωριστό κεφάλαιο για την κεφαλαλγία από κατάχρηση αναλγητικών.

Η ψυχιατρική διάσταση, η αναφορά στα κέντρα κεφαλαλγίας, η χρήση ημερολογίου κεφαλαλγίας και η προσπάθεια κατάρριψης μύθων και παραπλανητικών γνώσεων είναι από τα ευχάριστα ευρήματα στο βιβλίο που συνοδεύεται και από επιλεγμένη βιβλιογραφία.

Τέλος το τελευταίο κεφάλαιο για τις απόψεις των ασθενών και τις δράσεις τους είναι μια ευχάριστη αλλά και ενδιαφέρουσα έκπληξη. Δε μπορεί κανείς να μη σταθεί στην ιδιαίτερα αξιέπαινη, κουραστική, επιμελημένη και χρήσιμη προσπάθεια του συλλόγου των ασθενών με ημικρανία και κεφαλαλγία Ελλάδος. Η ποιοτική ενημέρωση που προσφέρει στους ασθενείς, αλλά και σε κάθε ενδιαφερόμενο με την καλαίσθητη και φροντισμένη αυτή έκδοση είναι άξια συγχαρητηρίων και ελπίζω να έχει συνέχεια.

Ενημερωτικές Σελίδες...

# Συνέδρια - Ημερίδες - Συμπόσια - Επιστημονικές εκδηλώσεις

## 2022

- **9-13 Ιουλίου 2022: 14th European Epilepsy Congress**, Geneva, Switzerland
- **8 Σεπτεμβρίου 2022: Νευρολογικές παθήσεις στην ΠΦΥ διεπιστημονικές προσεγγίσεις, Ε.ΚΟ.ΓΕΝ.ΙΑ.**, Πόρτο Χέλι
- **24-25 Σεπτεμβρίου 2022: Το ταξίδι του ασθενούς**, ΕΛΛ.Α.ΝΑ., Αθήνα
- **26-28 Οκτωβρίου 2022: ECTRIMS 2022**, Amsterdam
- **10-13 Νοεμβρίου 2022: 10ο Πανελλήνιο Συνέδριο Αγγειακών Εγκεφαλικών Νόσων**, Θεσσαλονίκη
- **8-11 Δεκεμβρίου 2022: ΕΛΛ.Α.ΝΑ.**, Θεσσαλονίκη
- **24-26 Μαΐου 2023: 9th European Stroke Organisation Conference**, Munich Germany
- **15-18 Ιουνίου 2023: 34ο Πανελλήνιο Συνέδριο Νευρολογίας**, Αθήνα
- **1-4 Ιουλίου 2023: 9th EAN Congress 2023**, Budapest
- **15-19 Οκτωβρίου 2023: XXVI World Congress of Neurology**, Montreal