Acetazolamide In Idiopathic Intracranial Hypertension

ATROUNE L., BENALLAG S., HABCHI N. , DJAAFER M.

Neurosurgery Department Mustapha Pacha – Algiers-Algeria

***Corresponding Author: :** *ATROUNE L.,Neurosurgery Department , Mustapha Pacha University Hospital, Algiers, Algeria*

Received: December 03, 2023 **Accepted:** December 25, 2023 **Published:** January 13, 2024
Citation: *ATROUNE L., BENALLAG S., HABCHI N., DJAAFER M. .ACETAZOLAMIDE IN IDIOPATHIC INTRACRANIAL HYPERTENSION. OLCIAS Journal. Vol.1(2).*

Abstract:

Idiopathic intracranial hypertension (IIH) is defined by the existence of intracranial pressure greater than 15 mm Hg sustained. The clinical signs revealing an IIH are above all, headaches that are resistant to analgesics, jet vomiting and visual disturbances (papilledema, diplopia).

The objective of our study is to evaluate the use of acetazolamide in the management of IIH in hospitalized patients in our neurosurgery department. We retrospectively collected data from all patients admitted and managed for IIH from January 2007 to December 2020. 72 Patients were diagnosed with IIH, aged between 09 and 57 years old with an average age of 28 years old, 36% of our patients were aged between 20 and 30 years old. The sex ratio f/h was 8/1. Clinical manifestations of the IIH are those of any intracranial hypertension. Headache with nausea and/or vomiting is one of the major initial manifestations in most series as it was in ours: 88% headache, 12% vomiting and 10% diplopia.

Visual disorders are the most common complications of IIH, bilateral decrease in visual acuity was found in 49 patients (68% of our population) and one patient having bilateral blindness, bilateral papilledema was observed in 28 patients (46%) of which grades II, III, IV were 9%, 22%, 16% respectively, 7 patients had optic atrophy (9%). The fundus was without abnormality in 10 patients (11%). Brain MRI showed no abnormality in 46 patients (63%), cerebral imaging revealed an empty Sella turcica in 7 patients (7%), an arachnoidocele in 3 patients (4.5%), and an optic nerve anomaly in 4 patients (5.5%). acetazolamide was sufficient to normalize ICP in 6 patients. But surgical treatment had to be associated, it was necessary to perform a lumbar-peritoneal shunt in 47 patients (65.2%) and ventriculo-peritoneal shunt (VPS) in 17 patients (23.6%) due to the very high intracranial pressure (> 50CmH2O) and/or because of the visual impairment risk . When facing an abrupt appearance of papillary edema and oculomotor disturbances, associated with normal neuroradiological investigations, we must consider the diagnosis of IIH, start the treatment as quickly as possible in order to preserve the visual function.

Key words: *pseudotumor cerebri ; papillary edema, acetazolamide, lumbar peritoneal shunt*

Introduction:

Idiopathic intracranial hypertension (IIH), also called pseudotumor cerebri, is a disorder of unknown cause that results in a raised intracranial pressure (ICP) occurring in women of childbearing years. Obesity and weight gain are clearly established as related factors, as is female gender. IIH affects1–2 per 100,000 of the general population and 20 per 100,000 of the obese female population with numbers expected to rise over the forthcoming decade in line with escalating obesity figures (1). It should be noted that the term “benign” intracranial hypertension is relative because the prognosis of this pathology lies in the severity of visual impairment as it might end up in blindness in 10 to 30% of the cases (2). Acetazolamide is the most commonly used drug in IIH. Evidence has demonstrated modest improvement in visual field function in patients with IIH with mild visual loss (3,4).

Materials And Methods:

Population:

This is a retrospective study of the data collected from 72 patients that received medical and/or surgical treatment for IIH in our neurosurgery department from January 2007 to December 2017. We included in this series the patients who benefited from a cerebral imaging and whose file included the clinical state before the treatment, and a report specifying the method used for treatment.

Methods:

Neuro-imaging tests (Cranial CT scan, MRI, angio-MRI or arteriography, medullary MRI) were systematically performed in all patients to confirm the diagnosis and determine the etiology.

The ophthalmological assessment included a measure of visual acuity, an examination of the fundus, a study of ocular motility and visual field. ICP monitoring introduces notions of mean value, depression wave, thus the duration, a manometricc PL was used for measuring intracranial pressure (ICP); the medical treatment was based on acetazolamide Diamox®) and / or corticosteroid or on therapeutic abstention. Patients underwent surgical treatment which consisted of performing a lumbar peritoneal shunt (LPS) or Ventriculoperitoneal shunt (VPS). Demographic data (sex, age), clinical signs (ophthalmic and neurological symptoms, time of diagnosis, and CSF pressure), radiographic findings on cerebral MRI (empty sella turcica, distension of the subarachnoid space, and the presence of TSS on time-resolved contrast kinetics imaging (TRICKS), Fundus of the eye results (papillary edema, optic atrophy), visual acuity scoring and therapeutic strategies used (medical, neurosurgical and endovascular) were collected. Categorical variables were reported in terms of frequency and percentage.

Results:

Of a total of 98 patients followed for idiopathic intracranial hypertension, 72 met the criteria for this study. Our series includes 64 women (89%) and 8 men (11%). The average age of the onset of the first symptoms is 28 years old, ranging from 9 to 57 years. The sex ratio was 8F/1H. The common age group for women was 20 to 30 years old (36%). In our series 37 patients have no particular antecedents (51%) and a patient has thrombophlebitis (2%). The BMI (body mass index) at diagnosis was 35 ± 9.7 kg·m−2 (range: 17–68.7 kg·m−2) and 69% of patients had a BMI > 30 kg·m−2. The average time of diagnosis is 6 months with extremes of 15 days to 16 months. The most common diagnosis time was between 1 and 6 months.

Headache was the most common sign of call found in the initial assessment in 64 patients (88%). Other symptoms have also been observed, Such as vomiting (12%) and diplopia (10%).

Ophthalmological report:

Visual acuity: Visual acuity was estimated in all patients, 5 patients had 10/10 VA for both eyes, 49 patients had bilateral decrease in visual acuity (68%) and one patient has bilateral blindness.

Papillary edema: Bilateral papillary edema occurred in 28 (46%) cases, where grades II, III, IV were presented in 9%, 22%, 16% of our population respectively, 7 patients had optic atrophy (9%). The fundus of the eye was without abnormalities in 10 patients (11%).

An elevated intracranial pressure was documented during lumbar puncture measured in the lateral decubitus position. 24 hours intracranial CSF pressure monitoring was performed in 30 patients. Median CSF opening pressure was 350mmCSF (range: 150–540mmCSF) and (23%) patients presented a pressure below 250 mmCSF.

Cerebral MRI time-resolved imaging of contrast kinetics (TRICKS**)** revealed an abnormality of the Sella Turcica which is empty in 7 patients (7%), an arachnoidocele was found for 3 patients (4.5%), an optic nerve anomaly in 4 patients (5.5%), unilateral TSS or hypoplasia was found in 17 cases and Bilateral TSS in 2 cases. Brain MRI showed no abnormalities in 46 patients (63%).

Medical treatment using acetazolamide was initiated in 70 patients associated to potassium supplementation, while 2 patients didn't undergo any medical treatment (2.7%). Treated surgically in emergency, normalization of CSF pressure was obtained by lumbar puncture evacuations in 2 patients.

Surgical treatment

Lumbar-peritoneal shunt was performed in 75.4% of the cases; ventriculo-peritoneal shunt in 24.6% of the cases and a sub temporal decompression in 2 cases in second line after the first procedure.

In our population we had; Poor results in the 26% subgroup of patients with bilateral TSS, and those with a median CSF pressure superior to 350 mmCSF at the time of the diagnosis.

70 patients were treated with acetazolamide which were sufficient to normalize the pressure in 22,8 % the cases, while the rest needed the association of the surgical treatment.

A recurrence in 24% of the cases;

Complications related to the placement of the lumbar-peritoneal shunt were: catheter obstruction (7%); over-shunting (low pressure headaches) (13.8%); catheter migration (16%), lumbar radiculopathy (1.3%), and Chiari I malformation (1.3%).

Decrease in complication's rate after the introduction of flow-regulated valves**:** high-pressure valves possibly with an anti-siphon system to limit over-drainage**.**

Discussion:

In the late 1890's, Quince was the first to describe and name this syndrome "meningitis serosa". In 1904, Nonne termed this syndrome "pseudotumor cerebri" as the symptoms resembled a suspected intracranial mass. Foley (1955) renamed the condition "benign intracranial hypertension". However, in the late 1980's, Corbett altered the name to idiopathic intracranial hypertension, since the syndrome was not benign as it was once thought.
At present, idiopathic intracranial hypertension is the accepted designation.
Our series of 72 patients includes 64 women and 08 men. The sex ratio between women and men is 8/1.

The incidence would be 0.9 per 100,000 in the general population and 19.3 per 100,000 in women aged 20 to 44, with an addition of 20% or more depending on their ideal weight (5).
The physio-pathogenic mechanisms of the IIH are not fully understood. An increase in intracranial venous pressure, whatever the cause, could be the causal factor in many etiologies (6). This rise in intracranial venous pressure prevents the resorption of CSF by the increasing resistance (7,8) , a mechanism clearly involved during cerebral venous sinuses' thrombosis. A venous return obstruction may also be evoked in the presence of obesity (by elevation of the central venous pressure) as we observed (6,8) .
According to the modified Dandy criteria, an increase in CSF pressure (greater than 20 mm Hg), or a characteristic aspect of the curve during continuous recording of ICP, is always observed in the presence of IIH (9).
Weight loss is a crucial part of the treatment program, as even moderately obese patients may significantly benefit from it. The response to this treatment is generally satisfactory, resulting in a rapid normalization of the eyes' fundus.
More than 60 years ago, treatment for IIH was centered on the use of systemic corticosteroids. In 1961, Paterson et al (10) first reported a beneficial effect of steroids in 6 of 7 patients with IIH. In a review of the literature in 2010, Wall (11) stated: "Steroids are still occasionally used to treat IIH but their mechanism of action remains unclear." He went on to describe many of the side effects including weight gain in these typically obese patients.

Jefferson and Clark (12) discussed the use of diuretics such as furosemide as a potential treatment for IIH in the 1970s. It was well documented that furosemide could lower ICP by diuresis and reducing sodium transport into the brain (13, 11). Some including Hannerz (14) believed that weight loss due to digoxin might be a more plausible explanation, whereas others pointed out that the mechanism of action of digoxin in IIH remains uncertain (15).

Lastly The sulfonamide carbonic anhydrase inhibitor (CAI) acetazolamide (AAZ), a compound developed in the 1950s as a diuretic drug and presently used as an antiglaucoma, antiepileptic and diuretic agent; In the 1970s, Lubow and Kuhr (16) documented its use in a series of 40 patients (39 female with "primary idiopathic pseudotumor"). Gradually, acetazolamide became a preferred medical treatment of patients with IIH.

There are few pharmacologic interventions for the control of elevated ICP, a poorly understood neurologic syndrome. Treatment with the sulfonamide CAI AAZ seems to be the most used approach. The rationale for using AAZ for the treatment of IIH is based on the potent inhibitory action of the compound against some CA isoforms involved in the secretion of CSF by the choroid plexus.

The Carbonic anhydrases (CA) are metalloenzymes present in all life kingdoms, as they equilibrate the reaction between three simple but essential chemical species: CO2, bicarbonate and protons reaction (17,18) . They highly important in acid base equilibration and pH homeostasis in organisms all over the phylogenetic tree (17,19, 20,21) . CAs are involved in many crucial physiologic and pathologic processes connected not only to pH regulation but also to the secretion of electrolytes (bicarbonate, acid, etc), biosynthetic processes (gluconeogenesis, lipogenesis, ureagenesis), photosynthesis (in plants), tumorigenesis, etc. (17,19, 20,22, 23) .

Inhibition of the CAs has pharmacologic applications in many fields, such as antiglaucoma (24,25, 26) , anticonvulsant (24,27, 28) , antiobesity (24,29) and anticancer agents/diagnostic tools (20,24,, 30), although they were initially designed as diuretics(31) . Indeed, acetazolamide AAZ was the first nonmercurial diuretic to enter in clinical use in 1954, followed shortly thereafter by methazolamide (MZA) (FIGURE 1) (31).

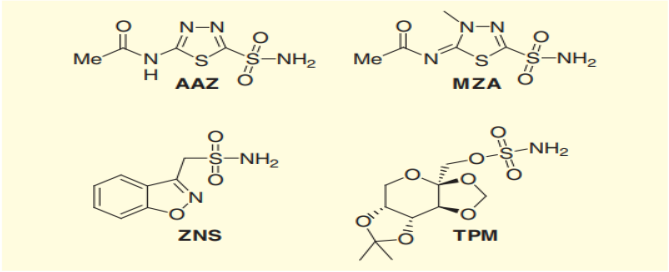


Figure 1. CAIs of the sulfonamide/sulfamate type in clinical use.
AAZ: Acetazolamide; MZA: Methazolamide; TPM: Topiramate; ZNS: Zonisamide.

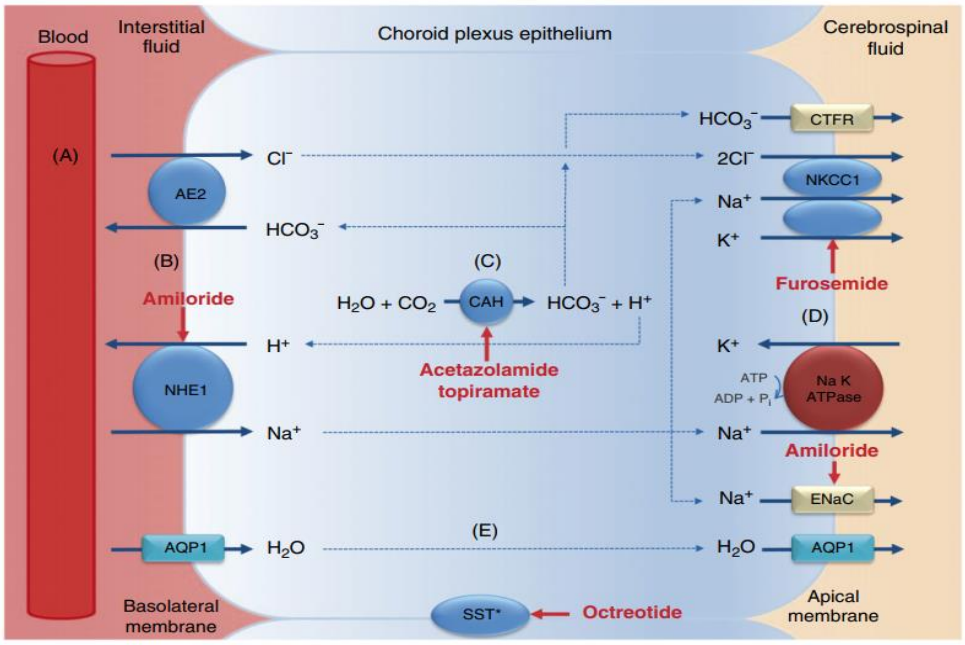
The human brain and the choroid plexus contain a multitude of CA isoforms, although their functions are still not completely understood (28) . The membrane-associated CA IV is located on the luminal surface of cerebral capillaries, and associated with the blood–brain barrier, being also concentrated in layers III and VI in the cortex, hippocampus and thalamus of all investigated mammals (28) .

The epithelial cells of the choroid plexus secrete CSF by a process which involves the transport of Na+, Cl and HCO3 from blood to the brain ventricles(32,33). This ion uptake establishes an osmotic gradient driving water secretion into the CSF.

Furthermore, this secretory process is highly dependent on several transporters of HCO3- expressed in the choroid plexus (34) . The first evidence that CA, which is highly active in the choroids plexus(35), plays
a role in the formation of CSF has been asserted by Davson, et al. in 1957(36).

The active site of CA XII is located outside the cell of the choroid plexus epithelium in front of the blood stream. Thus, this isoform may contribute to recycling the carbon dioxide into the epithelial cells, improving the transport of water and bicarbonate into CSF, working thus in concert with CA II in the production and flow of this fluid(32). The elevated intracranial pressure characteristic of IIH might therefore be assigned to the activities of CA II and CA XII, which are located and abundant in the choroid plexus.

Sulfonamides and their isosteres, such as the sulfamates, constitute the best investigated class of CAIs. These compounds bind in deprotonated state to the zinc ion from the enzyme active site, substituting the catalytic water molecule/hydroxide ion involved in the catalytic processes (17, 24). The scaffold of the inhibitors also participates in interactions with the enzyme active site, leading thus to a low nanomolar efficacy of many such compounds against most of the physiologically relevant CA isoforms.
It may be observed that AAZ is an effective inhibitor against all of them, similar to MZA, which is a weak hCA IV inhibitor, but an effective one, against the remaining isoforms. ZNS, an aliphatic sulfonamide used for the treatment of epilepsy (24, 28), is an ineffective CAI against hCA IV, XII and XIV, being much more effective against hCA II, VA and VII. The sulfamate TPM, another clinically used agent as an antiepileptic and antiobesity agent (24, 28), is also a weak inhibitor of hCA IV and XIV, but a very effective one of hCA II, VA, VII and XII. And since, the main isoforms involved in CSF formation are CA II and XII, and as these isoforms are highly inhibited byAAZ, MZA and TPM, these three clinical agents may be useful for reducing the increased ICP characteristic of IIH. (FIGURE 2) (37).



(FIGURE 2) CSF formation in the choroid plexus and potential sites of action of the commonly used drugs in IIH.

(a) Hydrostatic pressure drives the passive filtration of fluid from the blood through the fenestrated capillaries into the choroidal interstitial fluid. (b) At the basolateral membrane, ion exchangers substitute Hþ and HCO3 for Naþ and Cl respectively. (c) The carbonic anhydrase enzyme catalyses the conversion of H2O and CO2 to HCO3 and Hþ. (d) On the apical surface, the Naþ Kþ ATPase actively pumps 2Kþ in and 3Naþ out and the NaþKþ2Cl co-transporter, driven by the accumulation of Cl, moves 2Cl, Naþ and Kþ ions out. HCO3 and Kþ also passively move out of the cells. (e) The net movement of Naþ, Cl and HCO3 generates an osmotic gradient causing the movement of water in the same direction. Water moves mainly via a transcellular route, with aquaporin 1 at the basolateral and apical membrane facilitating water transport along this osmotic gradient. CAH: carbonic anhydrase; SST: somatostatin receptor (*location in the choroid plexus unknown); AQP1: aquaporin 1; NKKC1: Na-KCL cotransporter 1; NHE-1: Na-H antiporter 1; AE2: anion exchange protein 2; ENaC: epithelial Na channel.

The controversy surrounding the best medication to use in IIH led the Neuro-Ophthalmologic Research Disease Investigator Consortium (NORDIC) to organize a treatment trial. A multicenter, randomized, doublemasked, placebo-controlled study called the IIH Treatment Trial (IIHTT) was sponsored by the National Eye Institute (NEI). Its aim was to determine the value of acetazolamide and diet vs diet and placebo (38,39). It was a controlled study of weight-reduction and low sodium diet plus acetazolamide vs diet plus placebo in subjects with

mild visual loss. The IIHTT showed statistically significant effects of acetazolamide to: Improve visual field function, decrease papilledema grade , improve quality of life measures decrease CSF pressure.

The IIHTT concludes that Acetazolamide when used in IIH patients with mild visual loss produces a modest improvement in vision and it has its greatest effect on visual field function and papilledema in the first month of escalating dosage similar to our experience; while Acetazolamide-plus-diet patients lost twice as much weight as placebo plus-diet patients, the acetazolamide effect on visual loss was independent of the weight loss. Witch could explain the necessity for surgery in our patients who had issues losing weight as the effect of Acetazolamide alone was not enough.
Many IIHTT subjects tolerated maximal dosages of acetazolamide. While there were many expected side effects, quality of life measures were significantly better in the acetazolamide-plus-diet group. There was no permanent morbidity from acetazolamide use Similar to our series where the Positive acetazolamide-related effects on quality of life outweighed the side-effects of acetazolamide. However in IIHTT; IIH patients on acetazolamide as the only diuretic did not need potassium supplementation. While , in our study it was needed for all the patients.

As far as we know, few other medications belonging to the CAI pharmacologic class, apart AAZ, were investigated in clinical trials for the treatment of IIH, but the in vitro inhibition data analyzed in previous studies of several drugs may provide the rationale for using other agents, such as MZA, TPM and ZNS in future clinical trials for the management of IIH(40), Because we need to keep in mind that both acetazolamide and topiramate cause metabolic acidosis, by inhibiting carbonic anhydrase enzymes required for effective bicarbonate reabsorption in the kidneys (41), In the 2014 IIH Treatment Trial, patients were treated with acetazolamide up to 4 g daily, with an average adherence of 89% in the treatment group (42,43). Seventeen treated IIH patients (20%) experienced 23 metabolic adverse effects, including metabolic acidosis (n = 6), decreased appetite (n = 6), hyperchloremia (n = 4), hypokalemia (n = 4), and dehydration (n = 2) (42,43), hence why Individuals using acetazolamide for IIH should be monitored for electrolyte imbalances and tachypnea.

The repetition of evacuating lumbar punctures associated to acetazolamide sometimes allows a full recovery. The mechanism by which Optic nerve sheath decompression (ONSD) works has not been clarified. The lumboperitoneal (L-P) technique has traditionally been the method of choice if case of medical treatment failure.

Conclusion:

Given this evidence, it seems logical that when medication is being considered in patients with IIH with mild visual field loss, acetazolamide along with diet promoting weight loss must be considered the first-line therapeutic strategy in most cases. However medical and surgical treatment of patients with IIH is often challenging, requiring integration of the history, examination, and clinical course and The management approach should be tailored for each patient according to the severity of vision loss, severity of papilledema, severity of symptoms, response to medical therapy, and ability to tolerate medical therapy.

References :

1. **Markey KA, Mollan SP, Jensen RH, et al.** (2016).Understanding idiopathic intracranial hypertension: Mechanisms, management, and future directions. *Lancet Neurol ; 15: 78–91.*
2. **Brodsky MC, Vaphiades M.** (1998). Magnetic resonance imaging in pseudotumor cerebri. *Ophthalmology. ;1051686-93.*
3. **Ball AK, Howman A, Wheatley K, et al.**(2011). A randomized controlled trial of treatment for idiopathic intracranial hypertension. *J Neurol ; 258: 874–881*
4. **Wall M, McDermott MP, Kieburtz KD, et al.**(2014). Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: The idiopathic intracranial hypertension treatment trial. *Jama ; 311: 1641–1651*
5. **Biousse V., Bousser M.G.**(2001). L'hypertension intracrânienne bénigne. *Rev Neurol (Paris) ; 157 : 21-34*
6. **Karahalios DG, Rekate HL, Khayata MH, Apostolides PJ.**(1996). Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies. *Neurology ;46:198-202.*
7. **Drouet A, Valance J**.(1998). Hypertension intracrânienne bénigne et hypervitaminose A chronique. *Rev. Neurol ;154:253-6.*
8. **Seydou Bakayoko Nouhoum Guirou, Brainima Coulibaly et Jeannette Traoré** (2017).Œdème papillaire bilatéral secondaire à une hypertension intracrânienne chez une adolescente. *Pan Afr Med J.; 26: 123*
9. **Wall M, George D.** (1991). Idiopathic intracranial hypertension. A prospective study of 50 patients. *Brain ;114:55-80.*
10. **Paterson R, Depasquale N, Mann S.**.(1961) Pseudotumor cerebri. *Medicine (Baltimore). ;40:85–99*
11. **Wall M.**(2010). Idiopathic intracranial hypertension. *Neurol Clin. :593–617*
12. **Jefferson A, Clark J.**(1976). Treatment of benign intracranial hypertension by dehydrating agents with particular reference to the measurement of the blind spot area as a means of recording improvement. *J*

Neurol Neurosurg Psychiatry. ;39:627–639

13. **Pollay M, Fullenwider C, Roberts P, Stevens FA.**(1983). Effect of mannitol and furosemide on blood-brain osmotic gradient and intracranial pressure. *J Neurosurg. ;59:945–950.*
14. **Hannerz J.** (2001). Decrease of intracranial pressure and weight with digoxin in obesity. *J Clin Pharmacol;41:465–468.*
15. **Haagensen J, Hoegerl C.**(2014). Digoxin and a treatment for patients with idiopathic intracranial hypertension. *J Am Osteopath Assoc. ;114:213–215*
16. **Lubow M, Kuhr L.**(1976). Pseudotumor cerebri: comments on practical management. In: Glaser JS, Smith JL, eds. Neuro-ophthalmology. *Vol IX. St. Louis, MO: CV Mosby, :199–206*
17. **Supuran CT.** (2012). Structure-based drug discovery of carbonic anhydrase inhibitors. J Enzyme Inhib Med Chem ;27:759-72
18. **Supuran CT.** (2010).Carbonic anhydrase inhibitors. *Bioorg Med Chem Lett ;20:3467-74*
19. **Alterio V, Di Fiore A, D'Ambrosio K, et al.**(2012). Multiple binding modes of inhibitors to carbonic anhydrases: how to design specific drugs targeting 15 different isoforms *Chem Rev ;112:4421-68*
20. **Neri D, Supuran CT.**(2011). Interfering with pH regulation in tumours as a therapeutic strategy. *Nature Rev Drug Discov ;10: 767-77*
21. **Alp C, Ozsoy S, Alp NA, et al.**(2012). Sulfapyridine-like benzenesulfonamide derivatives as inhibitors of carbonic anhydrase isoenzymes I, II and VI. *J Enzyme Inhib Med Chem ;27: 818-24*
22. **Carta F, Scozzafava A, Supuran CT.**(2012). Sulfonamides (RSO2NH2): a patent review 2008-2012. Expert Opin Ther Pat ;22: 747-58
23. **Scozzafava A, Supuran CT, Carta F.** (2013). Antiobesity Carbonic Anhydrase Inhibitors: A Literature and Patent review. Expert Opin Ther Pat ;23:725-35
24. **Supuran CT.**(2008). Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. Nature Rev Drug Discov ;7: 168-81
25. **Carta F, Supuran CT, Scozzafava A.** (2012). Novel therapies for glaucoma: a patent review 2007-2011. Expert Opin Ther Pat ;22: 79-88
26. **Masini E, Carta F, Scozzafava A, Supuran CT.**(2013). Antiglaucoma carbonic anhydrase inhibitors: A patent review. *Expert Opin Ther Pat ;23:705-16*
27. **Aggarwal M, McKenna R.** (2008). Update on carbonic anhydrase inhibitors: a patent review. 2008;*Expert Opin Ther Pat ;22:903-15*
28. **Thiry A, Dogne` JM, Masereel B, Supuran CT**.(2007). Carbonic anhydrase inhibitors as anticonvulsant agents. *Curr Top Med Chem ;7:855-64*

29. **Supuran CT.**(2012). Carbonic anhydrase inhibitors as emerging drugs for the treatment of obesity. Expert Opin Emerg Drugs ;17:11-15
30. **Carta F, Temperini C, Innocenti A, et al.**(2010). Polyamines inhibit carbonic anhydrases by anchoring to the zinc-oordinated water molecule. *J Med Chem ;53:5511-22*
31. Carta F, Supuran CT.(2013). Diuretics with carbonic anhydrase inhibitory action: A patent and literature review (2005-2013). Expert Opin Ther Pat;23:681-91
32. **Halmi P, Parkkila S, Honkaniemi J.**(2006). Expression of carbonic anhydrases II, IV, VII, VIII and XII in rat brain after kainic acid induced status epilepticus. *Neurochem Int ;48:24-30*
33. **Milhorat TH, Hammocck MK.**(1983). Cerebrospinal fluid as a reflection of internal milieu of brain. Neurobiology of Cerebrospinal Fluid. *Plenum Press; New-York: pp 1-23*
34. **Brown PD, Davies SL, Speake T, Millar ID.**(2004). Molecular mechanisms of cerebrospinal fluid production. *Neuroscience ;129:957-70*
35. **Masuzawa T, Sato F.**(1983).The enzyme histochemistry of the choroid plexus. *Brain ;106(Pt1):55-99*
36. **Davson H, Luck CP.** (1957). The effect of acetazolamide on the chemical composition of the aqueous humour and cerebrospinal fluid of some mammalian species and on the rate of turnover of 24Na in these fluids. *J Physiol ;137:279-93*
37. **William J Scotton, Hannah F Botfield, Connar SJ Westgateand al.** (2019). Topiramate is more effective than acetazolamide at lowering intracranial pressure; Cephalalgia. *Vol. 39(2) 209–218*
38. *Wall M, Kupersmith MJ, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, Katz DM, Keitner JL, Schron EB, McDermott MP.* (2014). NORDIC Idiopathic Intracranial Hypertension Study Group. The idiopathic intracranial hypertension treatment trial clinical profile at baseline. *JAMA Neurol. ;71:693–701.*
39. **NORDIC.** (2014). Idiopathic Intracranial Hypertension Study Group Writing Committee, Wall M, Schron EB, Kupersmith MJ. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. J*AMA. ;311:1641–1651*
40. **Claudiu T Supuran.**(2015). Acetazolamide for the treatment of idiopathic intracranial hypertension, Expert Rev. *Neurother. Early online, 1–6*
41. **Pham AQ, Xu LH, Moe OW.** (2015). Drug-induced metabolic acidosis. *F1000Res. ;4:F1000 Faculty Rev-1460*
42. **Wall M, McDermott MP, Kieburtz KD, et al.**(2014). for the NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic

intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *JAMA. ;311:1641–1651.*

43. **Quick S, Linn D.**(2017). Chapter 18 diuretics. *Side Eff Drugs Annu. ;39:189–195.*