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DRUG-INDUCED CILIOCHOROIDAL EFFUSION SYNDROME: TWO CASE REPORTS AND A HYPOTHESIS FOR PATHOPHYSIOLOGIC MECHANISM

Ciliochoroidal effusion syndrome is a rare condition, characterized by ciliochoroidal effusion with ciliary body edema, shallow anterior chamber, acute angle closure glaucoma, myopic shift and lens thickening. [1] The etiology of this syndrome can be ocular inflammation, venous congestion, postoperative status, neoplasia, trauma, drug-intake or idiopathic. [2] In case of systemic diseases or drugs, the syndrome presents itself bilaterally. A list of drugs known to cause this syndrome can be found in table 1.

DRUG CLASS	DRUG
Sulpha-derivatives	Topiramate [3] Acetazolamide [4] Hydrochlorothiazide [5] Cotrimoxazole [6] Chlorthalidone [7] Indapamide [8] Sulphanilamide [9] Ethoxzolamide [10]
Aspirin-derivatives	Acetylsalicylate [11] Mefenamic acid [12]
Other drugs	Venlafaxine [13] Metronidazole [14] Aripiprazole [15] Levomepromazine [16]

Mainly sulpha-derivatives have been described as having the capacity to cause ciliochoroidal effusion syndrome. Topiramate in particular has been mentioned in a lot of case reports as the causal agent of the syndrome [3], sometimes referred to as TABAC (Topiramate Associated Bilateral Angle Closure glaucoma). [17] Several other drugs such as glibenclamide, promethazine, spironolactone, tetracasactrin, isosorbide dinitrate, tetracycline, penicillamine, quinine and isotretinoin have also been related to this syndrome [18] but the causal relationship is less clear since the authors of these articles only mention myopisation but no choroidal effusion nor narrowing of the anterior chamber.

★ CASE REPORTS ★

Case 1

A 43-year old man presented in our clinic after noticing bilateral reduced distance vision on awakening. When he was seen in emergency, he started suffering from a bifrontal headache. His relevant medical history was previous alcoholism, polyneuropathy, bipolar disorder, epilepsy, an orbital fracture 10 years previously and a tremor. When the tremor was too severe, he sometimes used valproic acid (Depakine® 500mg) but it had already been three weeks since he last took this drug. He had however recently taken several tablets of acetylsalicylate (Aspirin® 400mg), suffering from a minor headache. Visual acuity was 1.0 right eye and 0.9 left eye with -2.75 dioptre en -2.25 dioptre respectively.

Applanation tonometry was 36 mm of mercury for both eyes. Biomicroscopy showed bilateral very narrow anterior chambers with angle closure in combination with an anterior displacement of the lens-iris diaphragm. No iris bombans was seen. Fundoscopy after dilation showed a normal optic disc and macula in both eyes. No choroidal detachment was seen although an edematous retina was noticed bilaterally inferior. A B-scan of both eyes (see figure 1) showed bilateral thickened choroids and little choroidal effusion (not visible on these outprints).

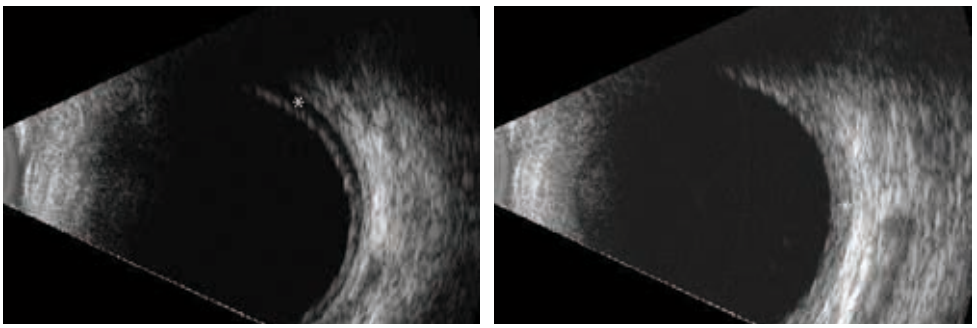

Figure 1: B-scans of the right (OD) and left (OS) eye. (*) Thickened choroid

The patient was treated with brinzolamide/timolol maleate fixed combination eye drops 2 times a day, acetazolamide 2 times 250 mg orally a day and methylprednisolone 64 mg orally a day. As there was no obvious cause for this ciliochoroidal effusion syndrome, an internistic workup was done to check for HIV, herpes zoster infection, IgA nephropathy, syphilis and systemic lupus erythematosus. [19] All examinations came back negative. The patient was seen the following day and intraocular pressure had returned to normal in combination with a deepened anterior chamber and a nearly emmetropic refractive status. A fluorescein angiography was performed which showed no abnormalities. All drugs were stopped and steroids could quickly be tapered off.

Case 2

A three year old girl with no important medical history presented in emergency with blurry distance vision. The girl had started taking medications for pansinusitis two weeks earlier (see table 2). After two weeks, the parents noticed that the girl had started keeping everything very close to look at. They suspected a relation with the recently started medical therapy for the pansinusitis and therefore stopped all medication. Two days later, the parents observed that the girl was still displaying very myopic behavior and decided to call for an urgent ophthalmic appointment.

Medication (Mark, Manufacturer)	Dose	Administration
Budesonide (Rhinocort, AstraZeneca)	64 µg/dose	Nosespray (2 times/day)
Carbocisteine (Sirox̧l, Melisana)	100mg/5ml	Orally (2 times 5ml)
Nasal aerosol (Rinoflow)	8ml	2 times/day, one minute
Broomhexine/hydrochloride (Bisolvon, Boehringer Ingelheim)	2mg/ml	Aerosol (1ml)
Ipratropiumbromide (Atrovent, Boehringer Ingelheim)	0.25mg/2ml	Aerosol (2ml)
Thiamfenicol, glycinaatacetyl-cystenaat (Fluimucil, Zambon)	100mg/1ml solvent	Aerosol (1ml)
Physiological serum		Aerosol (4ml)

On examination, visual acuity was 1.0 both eyes (Kay pictures at two meters) with correction -9 dioptre. Applanation tonometry was 8 and 10 mm of mercury for the right and left eye respectively. Automatic refraction after cycloplegia revealed spherical equivalent -8.5 dioptre right eye and -9 dioptre left eye. Biomicroscopy showed bilaterally a narrow anterior chamber with a mild mydriatic pupil. No iris bombans was seen. Fundoscopy after dilation revealed bilaterally a normal optic disc and posterior pole. Glycemia was 86 mg/dl. A B-scan of the two eyes showed bilateral choroidal effusion (see figure 2).

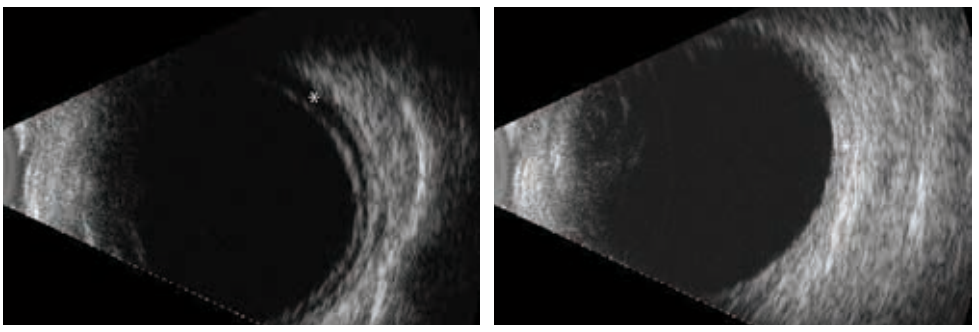

Figure 2: B-scans of the right (OD) and left (OS) eye. (*) Suprachoroidal fluid

The combination of myopisation, choroidal effusion and anterior chamber narrowing led us to the conclusion that this girl had a ciliochoroidal effusion syndrome. A quick search was done to see if any of the administered drugs had already been described as a cause of a ciliochoroidal effusion syndrome,

which was not the case. The parents had already stopped all medical therapy two days before the examination. We recommended to keep abstaining from all drugs in combination with cycloplegia. Already the following day, automatic refraction under cyclopegia showed a major reduction in myopia, i.e. -3 dioptre and -3.75 dioptre for the right and left eye respectively. Biomicroscopy showed a markedly deeper anterior chamber.

★ DISCUSSION ★

Two cases of a ciliochoroidal effusion syndrome have been presented. Case nr 1 was suspected to be caused by Aspirin since acetylsalicylate is known as a possible drug that can evoque this syndrome. [11] The patient from case nr 2 was on 5 different drugs, none of them being previously described as a possible cause of ciliochoroidal effusion syndrome.
Atrovent® is known to possibly elicit an acute angle closure glaucoma but based on a mechanism of pupillary block. Looking at the molecular structure of the other drugs used by the child, thiamphenicol does contain a methylsulphonyl group, resembling the structure of the sulphonamides. We do suspect that thiamphenicol was the cause of the ciliochoroidal effusion syndrome in case nr 2. judging by the results, NPDS was an excellent choice in these cases.

Differential diagnosis

Differential diagnosis of a ciliochoroidal effusion syndrome should include primary angle closure glaucoma (PACG), ciliary muscle spasm and malignant glaucoma. Differential diagnosis with PACG is made by the absence of a pupillary block. Also, a PACG does not usually present itself simultaneously bilateral. Differential diagnosis with ciliary muscle spasm is made by comparing the automatic refraction before and after cycloplegia, which is not markedly different in a ciliochoroidal effusion syndrome. Differential diagnosis with malignant glaucoma is less obvious since both conditions seem to have similarities in their presentation. Malignant glaucoma also presents as a shallowing of the central anterior chamber with anterior displacement of the lens-iris diaphragm, causing a myopic shift, in absence of a pupillary block. Malignant glaucoma though is usually related to intra-ocular surgery and does not present itself as simultaneous bilateral unless for example bilateral iridotomies have been performed. [20]

Pathophysiologic mechanisms

Proposed pathophysiologic mechanisms in literature

Several pathophysiologic mechanisms for a drug-induced ciliochoroidal effusion syndrome, more specifically by topiramate, have been proposed. Firstly, it has been suggested that an idiosyncratic reaction for sulpha-derivatives causes choroidal effusion. These drugs could work as a hapten, which implies

that drug metabolites bind to proteins and these altered proteins are perceived as foreign and induce an immune response. [21] Gubbay proposes that weak inhibition of carbonic anhydrase by topiramate is the cause of topiramate induced myopia. [22] Krieg and Schipper propose that a disturbance in the eicosanoid metabolism is the cause of ciliary body edema. [18] Another suggested cause for a ciliochoroidal effusion syndrome is a breakdown of the blood-ocular barrier in combination with a disruption of the blood-brain barrier since increased protein content in the cerebrospinal fluid (CSF) has been observed in a case of ciliochoroidal effusion syndrome caused by topiramate. [23] It might be that a ciliochoroidal effusion is dose dependent since it sometimes manifests itself after raising the dose of the inciting drug. [3] Rechallenging with the same drug, but at a lower dose does not elicit a new episode of myopisation nor angle closure, so a mechanism based on allergy seems very unlikely. [18] [22]

New hypothesis for pathophysiologic mechanism

We would like to propose a new mechanism by which drugs, and sulphonamides in particular, can cause a ciliochoroidal effusion syndrome. Our hypothesis is based on several observations. Firstly, because of the action-reaction principle, the pressure pushing the effusion into the supra-ciliochoroidal space must exceed the pressure in the vitreous cavity (which is in normal circumstances about the IOP measured by applanation tonometry).

Secondly, transportation of fluid across the ciliary body epithelium is among the highest in the human body [24], so if the inflow and outflow mechanisms of fluid were to be disturbed, edema would develop quickly. Civan and Macknight elucidated the mechanism on how aqueous is produced. [25] Furthermore, this fluid has to be transported across the nonpigmented epithelial cells because tight junctions, that form the bloodaqueous barrier, eliminate paracellular passage of water. Water leaves the non-pigmented epithelial cells to enter the posterior chamber in part through aquaporin (AQP) number 1 and 4 situated in the nonpigmented epithelial cells. [26] We propose that inflow of fluid in the ciliary body exceeds the transport capacity of fluid over the nonpigmented ciliary body epithelium. It is known that acetazolamide inhibits gene expression and water transport function of AQP1. In Lewis lung carcinoma, in which AQP1 is upregulated, topiramate inhibits carbonic anhydrase and decreases AQP1 expression. [27] This may mean that, in some prone individuals, fluid is limited in its transportation from the ciliary body into the posterior chamber by a reduction in function and expression of AQP1. Since the inflow of fluid into the ciliary body remains high and clearance of water out of the ciliary body is limited, ciliary body edema develops, eventually leaking into the normally virtual supraciliary and suprachoroidal space leading to ciliochoroidal effusion and exceeding the maximum transport capacity of fluid over the sclera. We find support for our theory in the fact that an increased protein content has been found in the CSF in a case of a ciliochoroidal effusion syndrome caused by topiramate. [23] Production of CSF in the choroid plexus also involves passage of water across AQP1 [28] and a reduction in water passage through the choroid plexus would lead to an increased protein content

per unit of CSF since less water is transferred to the CSF. We also find support for our theory since rats that develop a decreased function of AQP1 shortly after they are born exhibit a shallowing of the anterior chamber and in some cases apposition of the iris and cornea. [29] This finding is similar to anterior chamber narrowing in a ciliochoroidal effusion syndrome. Our theory also explains why a sulphonamides-induced ciliochoroidal syndrome only manifests itself after a couple of days: it takes some time before decreased AQP1 expression manifests itself since there are still enough AQP1 proteins working the first days after starting the drug.

We do not know whether our proposed theory of obstructed outflow of fluid out of the ciliary body into the posterior chamber also applies for drugs other than sulphonamides that have been described to cause a ciliochoroidal effusion syndrome. Salicylates for example have been shown to downregulate AQP6 expression in cochlear epithelium but not AQP1 nor AQP4 [30]. It may be possible that for nonsulphonamide drugs, other mechanisms than obstruction of outflow lead to a ciliochoroidal effusion syndrome. A substantial increase of inflow into the ciliary body, determined by six variables in Starling's equation, could also exceed the maximum outflow capacity of the ciliary body and, therefore, lead to a ciliochoroidal effusion syndrome. It is possible that for some drugs, inflow of fluid into the choroid exceeding the maximum outflow capacity is the inciting cause of a ciliochoroidal syndrome instead of the same disequilibrium at the ciliary body. Anterior chamber shallowing for example, has also been observed after retinal photocoagulation [31] and for these cases, one would expect that congestion of the choroid and not the ciliary body is the cause for the shallowing of the anterior chamber. Case nr 1 for example showed choroidal thickening in contrast to case number two. It is possible that leakage from the choroid was the cause for this ciliochoroidal effusion syndrome. Another explanation is that the IOP in the vitreous cavity increased even further after the anterior chamber closed, pushing the fluid into the choroid. Unfortunately, we did not perform an ultrasound biomicroscopy, so we don't know whether there was ciliary body edema or not. Since most authors, however, mention ciliary body edema and not choroidal edema in cases of a drug-induced ciliochoroidal effusion syndrome, we believe that in most cases ciliary body edema leads to the supra-ciliochoroidal effusion. As to why sulphonamides cause a ciliochoroidal effusion syndrome in some individuals and not in others is unclear. It is possible that there is a more pronounced reduction in AQP1 gene expression in these individuals. Another possibility is that other proteins involved in transportation of fluid across the nonpigmented ciliary body epithelium are deficient and that this is only noticeable when there is a downregulation of AQP1 function.

If indeed fluid is, as we propose, leaking from the ciliary body into the supra-ciliochoroidal space, the pressure pushing it into this space would be the pressure gradient between the ciliary body stroma and the posterior chamber. This pressure gradient is estimated to be more than 15 millimeters of mercury higher than the intraocular pressure. [32] This pressure gradient would push the vitreous forward, transferred by the ciliochoroidal fluid that is trapped between the sclera and the blood-retina barrier. Increased pressure on the vitreous causes it to push against the lens. This pressure gradient is partially

relieved by anterior movement of the lens-iris diaphragm. An equilibrium develops where IOP in the anterior chamber plus the force needed to displace the lens-iris diaphragm equals the IOP in the vitreous (e.g. case nr 2). It is important to realize that the pressure in the vitreous cavity in these circumstances is higher than the pressure measured by applanation tonometry. If before this equilibrium is reached, the anterior chamber angle closes (caused by a more anterior displacement of the lens-iris diaphragm and/or narrower anterior chamber in some individuals), IOP in the anterior and posterior chamber starts exceeding the raised IOP in the vitreous that started the process (e.g. case nr 1). As there is a swelling of the ciliary body, there is probably also a swelling of the iris root, further contributing to closure of the anterior chamber angle. Figure 3 shows our proposal for the pathophysiologic mechanisms that lead to a ciliochoroidal effusion syndrome. It has been shown that the myopic shift is mainly attributable to the anterior shift of the lens-iris diaphragm and to a lesser extent to the thickening of the lens. [33]

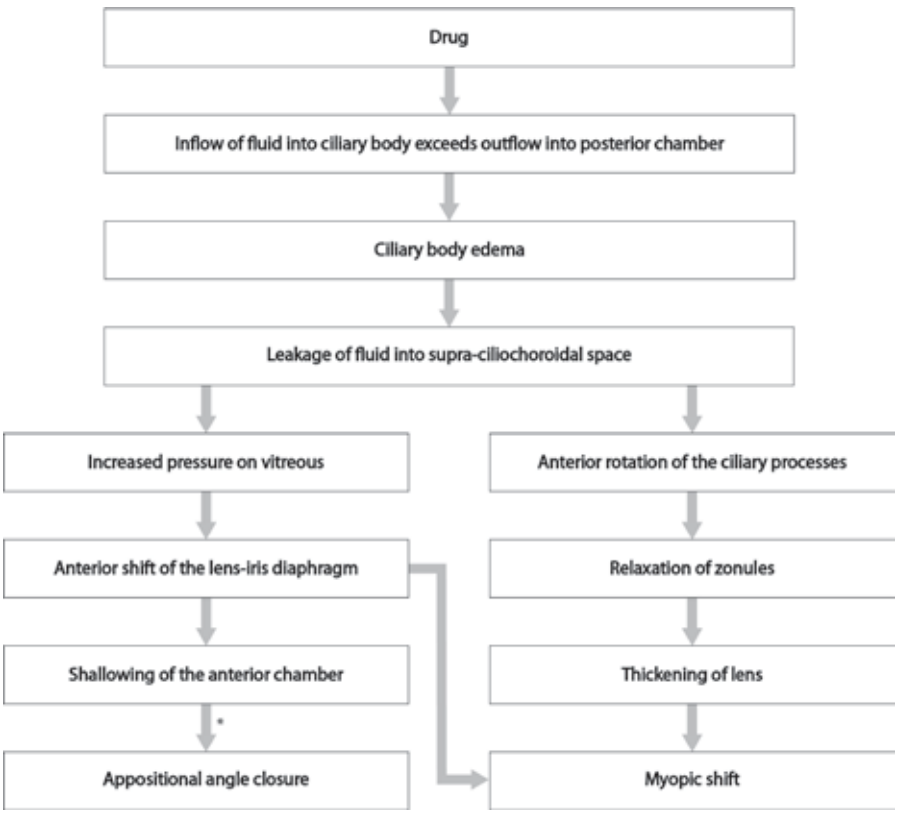

Figure 3: Postulated pathophysiologic mechanisms for a drug-induced ciliochoroidal effusion syndrome. (*) Only in case of more pronounced anterior chamber shallowing and/or narrower anterior chamber.

Therapy

When a ciliochoroidal effusion syndrome is encountered, all drugs taken by the patient should be checked and particularly sulpha-derivatives should be looked for. [1] Stopping the inciting drug will cause the syndrome to resolve in the following days. Medical therapy of a ciliochoroidal effusion syndrome consists of osmotic agents, anti-inflammatory drugs, cycloplegics and aqueous suppressants. Osmotic agents such as mannitol and glycerol remove fluids from

the entire eye but have a disproportionately greater effect on the choroid since this is the tissue closest to the vessels through which the hyperosmotic bolus passes. [34] Therefore they reduce choroidal expansion. Topical or systemic steroids may help reduce ciliary body swelling if an inflammatory component is suspected. Topical cycloplegics pull the anteriorly displaced lens backwards by tightening the zonules. Pilocarpine should be avoided as this may cause an anterior displacement of the lens-iris diaphragm and may aggravate the narrowing of the anterior chamber. Iridotomy is of no use since the rise in IOP is not caused by a pupillary block. Aqueous suppressants such as oral acetazolamide, topical beta-blockers and alpha-agonists reduce aqueous production and help reduce IOP in case of angle closure. Since acetazolamide itself is a sulpha-derivative, it seems unclear whether it should be used when the ciliochoroidal effusion syndrome is caused by another sulphaderivative. When a ciliochoroidal effusion syndrome caused by a sulphaderivative was treated with acetazolamide (with concomitant osmotics), this did not seem to worsen the condition or slow down recovery. [35] Apparently, therefore, there is no cross reaction between different sulpha-derivatives and it is safe to use acetazolamide in a case of ciliochoroidal effusion syndrome caused by another sulphaderivative. When however, a case was treated with acetazolamide without concomitant osmotics, this seemed to delay recovery. [36] So it seems reasonable not to use acetazolamide in a case of ciliochoroidal effusion syndrome with angle closure, but to use other aqueous suppressants (topical beta-blockers or alpha-agonists).

★ CONCLUSION ★

Ikeda was the first to name the combination of ciliochoroidal effusion with ciliary body edema, shallow anterior chamber, acute angle closure glaucoma, myopic shift and lens thickening as a ciliochoroidal effusion syndrome. [1] [2] Some drugs, especially sulpha-derivatives, and several local or systemic diseases can lead to this syndrome. [2] We propose that the cause for a drug-induced ciliochoroidal effusion syndrome is inflow of fluid into the ciliary body exceeding the transport capacity of fluid over the nonpigmented ciliary body epithelium. This disequilibrium would lead to ciliary body edema leaking into the supra-ciliochoroidal space, pushing the vitreous forward. Encountered with a bilateral shallowing of the anterior chamber and myopic shift, a careful history of medication intake is necessary as well as an echo B-scan and ultrasound biomicroscopy to rule out choroidal expansion and ciliary body edema.

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