



### Idiopathic Intracranial Hypertension: a unifying neuroendocrine hypothesis is possible?

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#### Abstract

The clinical syndrome idiopathic intracranial hypertension (IIH), also termed pseudotumor cerebri, consists of symptoms of headache, nausea, vomiting and visual field defects in combination with findings of papilledema. IIH is commonly seen in overweight, 20–50-year-old women where the rise in intracranial pressure is putatively a consequence of an endocrine-based disturbance of electrolytes. Associated risk factors include primary and secondary aldosteronism, pregnancy, corticosteroid therapy and Cushing disease. Herein, we review the association between these conditions and IIH working toward its having a unifying neuroendocrine hypothesis.

#### Introduction

Idiopathic intracranial hypertension (IIH; also known as pseudotumor cerebri) is a neurological disorder of uncertain etiology, characterized by increased intracranial pressure in the absence of a tumor, hydrocephalus and no apparent cause evident on neuroimaging or other routine evaluation. Its main symptoms and signs are headache, nausea and vomiting, as well as visual field defects and papilledema. Its pathophysiologic origins remain uncertain.

Several decades ago, it was suggested IIH is a consequence of an underlying endocrine abnormality related to a disturbance of electrolytes. In 1955, Foley<sup>1</sup> suggested that: "...an underlying endocrine imbalance, with presumably a disturbance of electrolytes, is in some way connected with the alteration of intracranial pressure." The occurrence of a "...water-electrolyte imbalance, brought about by hormonal disturbance" was likewise suggested by Oldstone.<sup>2</sup>

In this context, Weber KT, et al. in 2002 were the first to draw attention to the association between IIH and primary aldosteronism (PAL) in 2 overweight, middle-aged women.<sup>3</sup> Since then additional cases associated with PAL have been reported.<sup>4</sup> IIH has also been reported in children and adolescents with secondary aldosteronism (SAL) from the UK including an Italian girl we recently reported.<sup>5</sup> The English literature thus currently consists of 12 reported cases of IIH with either PAL or SAL. The PAL group were mostly hypertensive middle-aged women with adrenal pathology, whereas the SAL patients were mostly normotensive girls affected by inherited renotubular defect. Five out of the 12 patients reviewed were treated with spironolactone with good control of symptoms. In two of these five, an additional therapy was correction of hypokalemia and hypomagnesaemia. The study conclusions inferred that IIH patients should be evaluated for aldosteronism and considered for spironolactone therapy.

#### Aldosteronism

Aldosterone is a mineralocorticoid which promotes Na<sup>+</sup> resorption at the expense of a well-recognized K<sup>+</sup> excretion and a less-recognized mechanism of Mg<sup>2+</sup> and Ca<sup>2+</sup> excretion in classic target tissues (e.g., kidneys, colon, and sweat and salivary glands) but also newly discovered sites including epithelial cells of the choroid plexus and inner ear.<sup>6, 7</sup> The biological action of aldosterone on the epithelial cells of the choroid plexus are similar to the classical mechanisms involved in the epithelial cells of the kidney (i.e., enhancement of the number and activity of the Na<sup>+</sup>/K<sup>+</sup> ATPase pumps in the apical membranes).<sup>8, 9</sup> Cerebrospinal fluid (CSF) production by the choroid plexus is governed by the systemic volume control, which is tightly regulated by the action of aldosterone acting on its specific receptors (Figure 1).<sup>10</sup> In this respect, aldosterone alters the composition of CSF, which in turn contributes to the regulation of blood (CSF) pressure.<sup>8</sup> Whether CSF formation is increased in aldosteronism accounting either for increased intracranial pressure and for headache, shared symptoms in aldosteronism and IIH, remains unknown.

In addition to aldosterone, other risk factors associated with IIH include pregnancy, corticosteroid therapy, Cushing disease, r Gh therapy, obesity and vitamin A intoxication, which act to enhance the renin-aldosterone axis thus disturbing the electrolyte balance and/or by influencing mineralocorticoid receptors in the epithelial cells of the choroid plexus.

#### Pregnancy

In normal pregnancy plasma aldosterone concentrations increase in parallel to progesterone<sup>11</sup> playing a key role in the maintenance of volume expansion (especially during the first trimester) by contributing to water and sodium retention. Progesterone has an additional effect secondary to its in vitro demonstrated high affinity for mineralocorticoids and its in vivo demonstrated low agonistic mineralocorticoid activities.<sup>12</sup> It is well known that IIH can be precipitated by normal pregnancy and that there is a tendency for preexisting IIH to worsen during pregnancy, possibly due these hormonal changes.<sup>13</sup> It is conceivable that the activation of the renin-aldosterone axis may have a pathogenetic role in pregnant women who develop IIH in association to their weight gain.

#### Corticosteroid Axis

Chronic steroid administration, Cushing disease and acute withdrawal of chronic steroid use are among the other largely reported risk factors for IIH. There is a putative mechanism for the effects of corticosteroids on CSF production. The enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) is highly expressed in the epithelium of the choroid plexuses: among its main activities is the reduction of inactive cortisone to cortisol. The latter can activate mineralocorticoid receptors with a degree of affinity similar to aldosterone thereby increasing CSF pressure and leading to the

development of IIH.<sup>14</sup> Of interest, it has been also proposed that autocrine regulation of intracerebral cortisol is dependent on 11 $\beta$ -HSD1 expression in the epithelial cells of the choroid plexus and that this enzyme may be involved in the CSF production and may influence cortisol levels in the CSF.<sup>15</sup> An additional effect of 11 $\beta$ -HSD2 is its dehydrogenase activity, which inactivates corticosterone or cortisol via their conversion to inactive cortisone. This enzyme in the adult brain is thought to protect mineralocorticoid receptors from activation by cortisol and it is also implicated in mediating central control of salt/water balance<sup>16</sup> where its expression in the brain could be considered a factor indirectly influencing CSF production and composition.

#### Renin/Aldosterone Axis and Obesity

The renin-aldosterone axis is involved and enhanced in obesity. Obesity is frequently associated with increased plasma aldosterone levels. Recent evidence suggests that human fat is a highly active endocrine tissue and secretory products strongly stimulate steroidogenesis in human adrenocortical cells (type NCI-H295R) with a predominant effect on mineralocorticoid secretion.<sup>17</sup> Human adipocytes secrete potent mineralocorticoid-releasing factors, suggesting a direct correlation between obesity and hypertension. Adipocytes release secretagogues that stimulate adrenocortical steroidogenesis with a strong effect on mineralocorticoid secretion. Mineralocorticoid-releasing factors secreted from subcutaneous or from visceral fat into the circulation may reach the adrenal glands via endocrine pathways reaching concentrations capable of stimulating adrenocortical steroidogenesis.<sup>18</sup> Increased levels of aldosterone may be responsible for hypertension and for cardiovascular complications associated with obesity, including IIH through the chronic stimulation of mineralocorticoid receptors in the choroid plexuses.

#### Vitamin A Intoxication

Recent studies focused on the role of retinoic acid during steroidogenesis and demonstrating that all-trans-retinoic acid (ATRA) activates the expression of neurosteroid biosynthesis genes in the human glial cell line Gl 1, expresses the major steroidogenic genes. Treatment with ATRA induces an increase in the expression of the cytochrome P450<sub>scc</sub> (CYP11A1) gene, the steroidogenic acute regulatory protein (StAR) and 3 $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ -HSD).<sup>19</sup> In addition, ATRA also induces de novo synthesis of neurosteroids, including pregnenolone and progesterone. These results would suggest that ATRA might induce the de novo neurosteroid synthesis via the induction of steroidogenic genes in human glial cells. The multiple effects of vitamin A on central nervous system functions might therefore be partly explained by the induction of neurosteroidogenesis by retinoic acids. Among the overall complications induced by vitamin A intoxication one could consider the risk of developing acute IIH, which could be related to an upregulation of the secretion of neurosteroids, which in turn would overload the mineralocorticoid receptor in the choroid plexuses.

#### Growth Hormone

Growth hormone (GH) has important effects on the renin-angiotensin-aldosterone system. Acute treatment of GH-deficient adults with r Gh can lead to sodium and water retention with increased plasma renin activity and aldosterone levels.<sup>20</sup> The complications of these treatment protocols include hypertension, dependent edema and carpal tunnel syndrome. In GH-deficient children treated with r Gh, hypertension-dependent edema and fluid retention are less frequent. However, some studies recorded transient, mild increases in blood pressure during the first phase of treatment.<sup>21</sup> Of interest, the activation of the renin/aldosterone axis complicated by sodium and water retention has been recorded in children with idiopathic short stature who had been treated with r Gh therapy.<sup>22, 23</sup> These findings suggest activation of the renin/aldosterone axis in children the exogenous (r Gh) hormone administration must overlap the endogenous (GH) hormone production. Recent studies have shown also that chronic GH excess is associated with increased aldosterone in humans and mice and that the underlying mechanism is likely to be independent from renin action, IGF I excess, or adrenal aldosterone synthase expression.<sup>24</sup>

#### A Unifying Neuroendocrine Hypothesis

The literature of reported cases of IIH points to various risk factors, together with yet unknown individual predisposition, as a cause of this neurological syndrome. The IIH has also been associated to conditions such as withdrawal of chronic steroid therapy<sup>25</sup>, hypoadrenalism<sup>26</sup> and vitamin A deficiency<sup>27</sup>; there are many reports that correlate these factors to an acute or chronic onset of IIH.

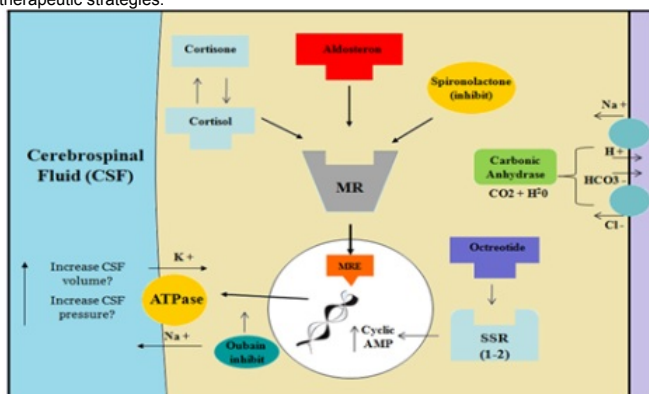
These conditions may reduce the activation of the MR in the epithelial cells of the choroid plexus resulting in a possible reduction of CSF volume and pressure.

Applying the Monroe-Kellie doctrine, which dictates that the sum and subtraction of the volumes of intracranial blood, cerebrospinal fluid, and cerebral tissue must remain constant where the skull is intact, a decrease in cerebrospinal fluid volume and pressure results in a reduction of CSF absorption in arachnoid villi and an increase in resistance to cerebrospinal fluid flow.

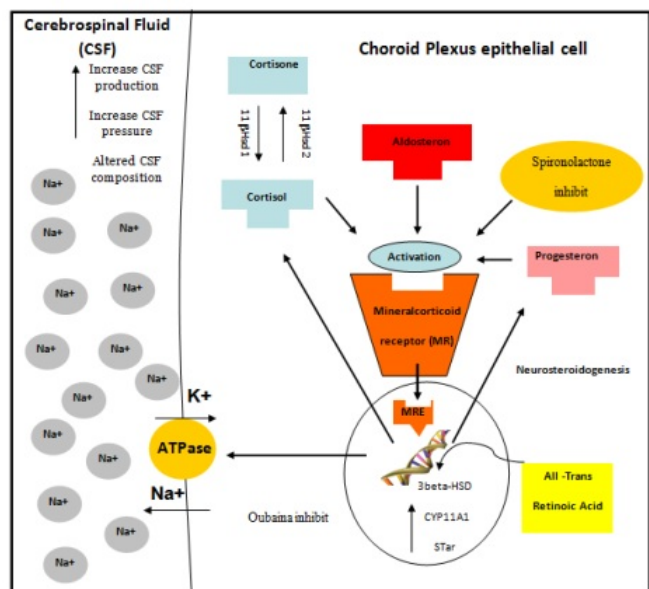
There is abundant evidence in support of this consideration. It has been shown in canine studies that the abrupt cessation of steroids after chronic therapy can cause a substantial reduction in cerebrospinal fluid absorption and a subsequent increase in resistance to cerebrospinal fluid flow.<sup>28</sup> Thus, abnormalities in cerebrospinal fluid dynamics during the glucocorticoid withdrawal may lead to high intracranial pressure.

We can imagine an impaired CSF outflow also in hypoadrenalism, with a similar mechanism. Vitamin A deficiency in experimental animals causes intracranial hypertension associated with a demonstrated increase in CSF outflow resistance. 29 Hyperaldosteronism, rGh therapy, Cushing disease, vitamin A intoxication, pregnancy and chronic steroid therapy could lead to IIH through CSF overproduction; on the contrary, vitamin A deficiency, acute withdrawal of chronic steroid therapy and hypoadrenalism could lead to IIH through prolonged reduction of CSF absorption (that exceeds the reduced production).

Thus far, however, there is not a credible and comprehensive hypothesis aimed to uncover the pathogenesis and pathophysiology of IIH despite the different mechanisms proposed. Some recent clinical and laboratory evidence have suggested a role for the renin/aldosterone system in symptomatic IIH patients: this was supported by the empirical benefits recorded after spironolactone (an antagonist of central receptors for aldosterone) administration. That could be regarded as the first etiological therapy in IIH. In addition there is an increasing number of evidence suggesting other hormones (e.g., corticosteroids, GH), endogenous or exogenous substances (e.g., retinoic acids) and/or enzymes (11 $\alpha$ -HSD1) may act on non-classical peripheral targets (i.e., epithelial cells of the choroid plexuses) involved in the production and increase of CSF. In light of these new advances we propose that multiple neuroendocrine interactions could influence the activation of mineralocorticoid receptor in the central nervous system and could play a key role in the onset of IIH. This awareness could provide the guidelines for a greater understanding of the underlying alteration of CSF production and composition (i.e., the main pathogenetic premise for developing IIH) and for non-conventional therapeutic strategies.



**Fig1.** Aldosterone, cortisol and progesterone can activate MR; spironolactone can antagonize this activation. In nucleus MR can activate mineralocorticoid responsive elements that stimulate synthesis from DNA of Na<sup>+</sup>/K<sup>+</sup> ATPase pumps. Oubain can inhibit activation and increased number of Na<sup>+</sup>/K<sup>+</sup> ATPase pumps. All-Trans retinoic acid, interacting with DNA, can activate neurosteroidogenesis and de novo synthesis of pregnenolone and progesterone.



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**Figure 1**  
**Figure Legend**

Figure 1 Aldosterone, cortisol and progesterone can activate MR; spironolactone can antagonize this activation. In nucleus MR can activate mineralocorticoid responsive elements that stimulate synthesis from DNA of Na<sup>+</sup>/K<sup>+</sup> ATPase pumps. Oubain can inhibit activation and increased number of Na<sup>+</sup>/K<sup>+</sup> ATPase pumps. All-Trans retinoic acid, interacting with DNA, can activate neurosteroidogenesis and de novo synthesis of pregnenolone and progesterone.