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The role of vitamin A and its CSF metabolites in supporting a novel mechanism of idiopathic intracranial hypertension

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Background

Elevated levels of retinoic acid (RA) may cause dynamic vitamin A metabolic and genetic transcriptional changes that will lead to decreased cellular viability, proliferation, cellular remodeling, adhesion changes and a resultant decrease in permeability, which contributes to elevated CSFP. RA and subsequent formation of retinyl esters, which act as surfactants may cause a toxic response in the arachnoid membrane leading to elevated CSFP.

Transthyretin (TTR) is a transport protein in blood and brain for BOTH vitamin A and RBP. TTR is also a critical transport protein for thyroxine, which is important in controlling metabolism and linked to obesity. The vitamin A transduction pathway links RBP, cellular retinoic acid binding protein (CRABP), TTR, retinol and RA.

Adipocytes are involved in retinoid metabolism and storage. (Okuno *et al*, 1995) This study even suggested that cellular retinol-binding protein (CRBP) gene expression is regulated dynamically in adipocytes by retinol uptake, intracellular transport and metabolism, which may be significant for the typical IIH patient (BMI > 30). The increased levels of adipocytes in these patients, which can dynamically regulate vitamin A metabolism by altering gene expression, are extremely important when trying to understand the etiology of this disease.

Methods

We prospectively obtained CSF and serum samples from 6 patients and 6 controls for analysis of RA, retinol, Retinol Binding Protein (RBP), and Transthyretin (TTR). Opening CSF pressures (OP) and BMI were obtained.

Results

No statistical differences were found between the mean ages or the BMI for these two groups. Patient OP obtained by radiologically-guided LP were statistically higher, mean 35.3 cm H_2O, vs 19.1 in Controls ($p < 0.0005$). Patient OP ranged from 25–48 and 8–23 among Controls. Patient means for both CSF total RA and CSF 13-cis retinoic acid were statistically higher ($p < 0.05$). Serum TTR/RBP approached significance ($p < 0.07$).

Conclusion

The results from this well-controlled clinical study which examined the CSF and serum of patients matched for BMI with and without IIH demonstrate significant elevations in CSF total RA and 13-cis-RA in IIH patients. There is also a trend toward significance for increased serum TTR/RBP in these patients. These data support our hypothesis for a significant role of vitamin A and its metabolites in the pathogenesis of IIH via directly altered metabolism and transcriptional regulatory changes in the arachnoid cells.