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REVIEW

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Cerebrospinal fluid biomarkers and genetic factors associated with normal pressure hydrocephalus and Alzheimer's disease: a narrative review

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Abstract

Background: Normal pressure hydrocephalus is a neurologic disease leading to enlargement of ventricles which is presented with gait and balance disturbance, cognitive decline, and urinary incontinence. Diagnosis of normal pressure hydrocephalus is challenging due to the late onset of signs and symptoms. In this review, we summarize the cerebrospinal fluid, plasma, pathology, and genetic biomarkers of normal pressure hydrocephalus and related disorders.

Body: Recently, cerebrospinal fluid and serum biomarkers analysis alongside gene analysis has received a lot of attention. Interpreting a set of serum and cerebrospinal fluid biomarkers along with genetic testing for candidate genes could differentiate NPH from other neurological diseases such as Alzheimer's disease, Parkinson's disease with dementia, and other types of dementia.

Conclusion: Better understanding the pathophysiology of normal pressure hydrocephalus through genetic studies can aid in evolving preventative measures and the early treatment of normal pressure hydrocephalus patients.

Keywords: Normal pressure hydrocephalus, Cerebrospinal fluid biomarkers, Genetic biomarkers, Alzheimer's disease, Dementia

Background

Pathological enlargement of the ventricles leads to hydrocephalus. The most common form of hydrocephalus involving adults is idiopathic normal pressure hydrocephalus (iNPH) in which brain imaging shows ventriculomegaly while the intracranial pressure remains within normal range with no determined secondary cause [1]. Patients with iNPH develop gait and balance disturbance as the most dominant symptom, often accompanied by cognitive decline and/or urinary incontinence. iNPH is diagnosed based on medical history, neurologic examination, and brain imaging with CT or MRI. The international iNPH guidelines and the Japanese iNPH guidelines described the diagnostic criteria for iNPH [2–4]. Neuroimaging, either CT or MRI, is an essential step in iNPH diagnosis. In iNPH, the lateral and third ventricles are enlarged with no obstruction. The Evans ratio or index is used to describe hydrocephalus and an Evans ratio greater than 0.3 indicates large ventricles. The annual incidence of iNPH is estimated to be 5.5/100.000. The iNPH prevalence among a population aged 65 is 3.7% and there is even a higher chance for people aged 80 years and above [5, 6].

The standard treatment for iNPH is through the cerebrospinal fluid (CSF) diversion from the craniospinal space to another anatomic space so the CSF can be reabsorbed [7]. Although patients with iNPH are characterized by impaired CSF dynamics, the specific etiology of

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iNPH is still unclear. Understanding the genetic-based pathways of iNPH provides valuable insight into the pathophysiology of the disease and could benefit us with further effective treatments and preventative measures. Diagnostic workup of iNPH can be challenging due to an overlap in symptoms and neuroimaging features with other differential diagnoses. Despite extensive investigations, a CSF biomarker profile in iNPH has not yet been identified [8]. This survey aims to summarize the main findings in this field which may help the better understanding of the etiology, diagnosis, and prevention of iNPH.

Main text

CSF, plasma and pathology biomarkers

Common biomarkers of Alzheimer's disease and NPH

The hallmark pathology of Alzheimer's disease (AD) is characterized by the lesions of amyloid-β (Aβ) plaques, tau proteins, and neurofibrillary tangles within the brain of patients [9]. These plaques accumulate in the brain and cause low levels of amyloid-β1–42 (Aβ 42) and an increase of neurofibrillary tangle formation, total tau (t-tau), and phosphorylated tau (p-tau) concentration in CSF. Whereas Aβ 42 had a lower concentration in CSF of AD patients, soluble amyloid-precursor proteins α and β (sAPPa, sAPPb), amyloid-β1–38 (Aβ 38), and amyloid-β1–40 (Aβ 40) were increased. Amyloid positron emission tomography (PET) tracers has high specificity for the detection of Aβ plaques. All of the amyloid peptides (Aβ 42, Aβ 38, and Aβ 40), sAPPa, sAPPb, p-tau, and total-tau protein were reduced in CSF of NPH patients compared to healthy controls and non-NPH patients [10–15]. We can use this comparison to differentiate between the two diseases but we must also pay attention to the comorbidity of these two diseases in interpreting these results. Improvement after surgical therapy in NPH patients may be associated with different AD-related biomarkers and this is inconsistent in studies. However, NPH patients who did not respond to therapy had positive PET results, lower Aβ 42 and higher t-tau level in CSF in a study conducted by Jang et al., but Müller-Schmitz et al. reported that patients who had NPH and AD-related CSF changes (high tau protein, high p-tau, low beta-amyloid) improved cognitive or gait functions after the spinal tap [16, 17]. The postoperative level of Aβ42 was similar in responder and non-responder patients to shunt surgery but non-responders had a high cortical level of Aβ42 [18]. The regional cerebral blood flow in the brain of NPH patients was significantly reduced compared to normal people and it was improved after surgery. The patients who had AD and NPH showed less improvement of regional cerebral blood flow after surgery compared to NPH only [19]. NPH Patients who had Aβ and tau protein in brain biopsy, CSF ventricular Aβ42 was lower and lumbar p-Tau was higher compared to those whom had not. Lumbar p-Tau was able to predict biopsy results for beta-Amyloid and tau protein. Patients with different biopsy profiles had not any difference in postoperative cognitive tests [20]. Reduction of Aβ42 level was seen in both AD and NPH but didn't differ between NPH and AD [8]. Indeed, the diagnostic value of Aβ42/Aβ40 ratio was higher than Aβ42 and it was reduced only in AD, while it was within the normal range in the sample of NPH and vascular dementia [21].

NFL

Neurofilaments are intermediate filaments that consist of light (NF-L), medium (NF-M), and heavy (NF-H) neuron-specific cytoskeletal components. NFs have an important role in axonal structural integrity. Neurofilament light chains are non-specific biomarkers in neurodegenerative and inflammatory diseases such as multiple sclerosis (MS) [22]. Neurofilament protein release in cerebrospinal fluid (CSF) and blood circulation occurs after Axonal damage [23]. Although Patients with NPH exhibited higher levels of NFL in the CSF compared to controls in numerous studies [24–27], it wasn't seen in the study by Jeppsson.A et al. [28]. In line with previous studies, it has been shown that NPH patients with more extensive periventricular white matter hyperintensities in MRI exhibited a high level of NFL in CSF before and after therapeutic surgery. It was shown that the greater reduction of NFL after surgery was correlated with better results on postoperative MRI and cognitive tests [24]. NFL can be used for differentiation of NPH from subcortical ischemic vascular disease along with other CSF biomarkers such as Aβ42, t-tau, and synaptic protein neurogranin (NG). These biomarkers were lower in the CSF of NPH patients compared to the CSF of patients with subcortical ischemic vascular disease [29]**.** The level of NFL in the CSF of the patients who only had NPH had no significant difference compared to the patients with NPH and AD or vascular diseases [21].

MBP

Myelin basic protein (MBP) is abundant in the central nervous system and has multiple functions such as binding to cytoskeleton proteins, myelination, and transmission of extracellular signaling [30]. Patients with NPH, neurovascular diseases, MS, and other neurometabolic disorders had high levels of MBP in CSF and blood samples [26, 31, 32].

LRG

Leucine-rich alpha-2-glycoprotein is localized within the extracellular matrix which binds to collagen, fibronectin,

and TGF β. LRG has a membrane-binding component and can potentially bind to transforming growth factor βI type II receptor (TGF βR-II) on the cell membrane. In the brain, LRG is expressed in astrocytes and pericapillary regions also, its expression is more in elderly than young patients [33]. According to this association NPH patients exhibited higher levels of TGF βR-II, TGF β, and LRG than healthy ones [34]. NPH patients had a higher level of LRG in CSF than healthy controls, but patients with Parkinson's disease with dementia (PDD) and progressive supranuclear palsy (PSP) exhibited a higher level of LRG than NPH and AD patients [35]. So far, studies have shown an increase in LRG in the CSF of NPH patients. LRG could be used as a potential biomarker for diagnosis and forecasting NPH improvement in patients after shunt surgery [36, 37].

Neuro-inflammatory biomarkers

Transforming growth factor β1 (TGF-β1) is a pleiotropic cytokine with multiple roles such as immunosuppression, anti-inflammatory effects, and synaptic plasticity. During an injury, TGF-β1 causes neurodegenerative neuroinflammation, vascular hypertrophy, and neural death [38]. Although TGF-β1 can trigger neuroinflammation, it is a known agent in neuroprotection in AD patients [39, 40]. As mentioned earlier, patients with NPH had high levels of βR-II, TGF β and LRG. The CSF level of TGF-β, and IL-1β is lower in NPH than AD [41, 42]. It has been shown that the CFS content of TGF-β1 in NPH was higher than patients with chronic obstructive hydrocephalus but not as significant as those with subarachnoid hemorrhage-induced hydrocephalus [43].

IL-1β, IL-6, IL-10 (anti-inflammatory cytokine) levels in CSF of NPH patients were significantly increased compared to healthy elderly but there was not any significance in serum levels [44]. These cytokines also increased in AD and Parkinson's disease (PD) and they were not disease-specific biomarkers [45].

Tumor necrosis factor-alpha (TNF-alpha) is probably linked to white matter. As its CSF level in NPH patients before shunt surgery was high and its reduction after surgery was correlated with cognitive improvement [46]. NPH patients had also an increased level of TNF-α compared to chronic obstructive hydrocephalus [44]. However, this relationship was not seen in further studies or was lower than the control group [45, 47]. Monocyte chemoattractant protein 1 (MCP-1) is a monocyte chemotaxis factor plays an important role in inflammation and its CFS level increases during NPH disease [10, 48]. Another inflammatory biomarker is Chitinase-3-like protein-1 (YKL-40) which is an astrocyte activation marker and increases in neuroinflammatory diseases like MS and AD. Previously, YKL-40 was used as a potential biomarker for discrimination of healthy persons and those with mild cognitive impairment and AD [49]. YKL-40 level didn't differ in NPH patients from patients with subcortical ischemic vascular disease [29]. However it could be a novel suggesting biomarker for differentiation of NPH from other mimics, but little is known about it [49, 50].

Other suggested biomarkers

Aquaporin 4 (AQ4) is a water channel in the CNS which is located on astrocytes to ease the CSF flow to the parenchyma of the brain [51]. Although it has recently been hypothesized that perivascular inflammation and decreased AQ4 levels in astrocytes may be involved in the pathophysiology of NPH, these changes were not due to CSF and serum level of AQP4-IgG/IgA/IgM auto-antibodies [52].

Protein tyrosine phosphatase receptor type Q (PTPRQ) is a protein associated with hearing loss. PTPRQ component of the CSF was higher in NPH patients than AD especially in shunt responder patients [53]. Analysis of NPH CSF metabolites showed a low level of glycerate and a high level of N-acetylneuraminate, serine, and 2-hydroxybutyrate compared to AD patients. Metabolite profile could be among novel markers for discrimination of these diseases [54]. The list of important CFS, plasma, and pathology biomarkers described is given in Table 1.

Genetic factors

CFAP43

Mutations in the gene encoding cilia and flagella associated with protein 43 (CFAP43) are connected to male infertility with various morphologic abnormalities of the sperm flagella. Studies have reported a strong association between the CFAP43 gene and the function and morphology of flagella [55, 56]. Primary cilia dyskinesia (PCD), is a disorder characterized by recurrent infection, hydrocephalus, and infertility [57]. The genetic evaluation of Japanese family members with NPH showed a nonsense gene mutation in CFAP43. The Cfap43−/− mice showed third and lateral ventricles dilation, disfigured sperm flagella, and excess cytoplasm in testis and epididymal cells. Also, a decrease in the number of acetylated tubulins (as a marker of cilium mortality) was found in the choroid plexus of Cfap43−/− mice. There was a defect of Spef2 (as a marker of the axoneme central pair) and Rsph4a (as a marker of radial spokes) in some of the epithelial cells of the lateral ventricle and trachea of the Cfap43−/− mice. Moreover, transmission electron microscopy analyses showed normal 9 + 2 axonemes in the cross-section of wild-type tracheal cilia mice but abnormal 8 or 10 + 2 peripheral microtubules in

Table 1 List of CSF, pathology and plasma biomarkers of NPH

Biomarker	Relation	References
Aβ 42, Aβ 38, and Aβ 40 sAPPa, sAPPb, p-tau, and total-tau protein	Decreased in NPH patients compared to healthy controls and non-NPH patients	[10–15]
Aβ42/Aβ40 ratio	Decreased only in AD, while it's within the normal range in NPH and vascular dementia	[21]
NFL	Increased in NPH compared to healthy controls	[24–27]
NFL, Aβ42, t-tau, and NG	Decreased in NPH patients compared to subcortical ischemic vascular disease	[29]
MBP	Increased in NPH, neurovascular diseases, MS, and other neurometabolic disorders	[26, 31, 32]
LRG	Increased in NPH, compared to healthy controls/increased in PDD and PSP compared to NPH and AD patients	[34, 35]
TGF-β1 and IL-1β	Decreased in NPH patients compared to AD	[41, 42]
IL-1β, IL-6, and IL-10 (anti-inflammatory cytokine)	Increased in NPH,AD and PD	[44, 45]
MCP-1	Increased in NPH compared to healthy controls	[10, 48]
AQ4	Decreased in NPH compared to healthy controls	[52]
PTPRQ	Increased in NPH compared to AD	[53]
Glycerate, serine, and 2-hydroxybutyrate	Lower level of glycerate and higher levels of N-acetylneuraminate, serine, and 2-hydroxybutyrate in NPH than AD	[54]

Cfap43-/-. Also, compound cilia were observed only in Cfap43−/− mice. In summary, mutations in the gene CFAP43 are responsible for ciliary dysfunction in different tissues such as the testis, epithelial cells lining the ventricles of the brain, choroid plexus, and also trachea [58].

Adenosine A1 and A2A receptors

The purine ribonucleoside adenosine (Ado) is produced extracellularly through catabolism of excreted ATP and intracellularly from AMP and then released by its transporter. Ado is a metabolite with vastly distributed throughout the body. Both extracellular and intracellular Ado levels increases in response to different physiological stimuli and inflammatory status and tissue injuries. Ado and G-protein are connected in contrary pathways: A1 receptor (A1R) connected to inhibitory Gi-protein and A2A receptor (A2AR) connected to excitatory Gs-protein, therefore decreasing and increasing cAMP levels, respectively. Ado receptors have a major role in brain vasculature dynamics [59]. Aside from brain perfusion, Ado receptors have a part in the control of brain inflammation and microglial activity [60]. Results from analysis of A1R and A2AR mRNA levels in peripheral blood mononuclear cells (PBMCs) from iNPH and control samples showed that the gene expression of A1R and A2AR in PBMCs was significantly lower in iNPH than control samples. The downregulation of A1R and A2AR gene and protein expressions in PBMCs from iNPH compared to healthy samples supports the involvement of the Ado system in the pathophysiology of iNPH disease [61].

Transthyterin and Amyloid precursor

AB peptide is a product of several cleavages of amyloid protein precursor (ABPP). ABPP is processed through cleavage by a secretase (ADAM9, ADAM10, or ADAM17) [62]. All pieces produced from AB processing have different participations in neural system activities [63]. Results from the genome expression profile from 22 iNPH patients and 8 non-demented control subjects showed a 17 fold decrease in Transthyretin expression in iNPH samples. Contrarily, ABPP was expressed three times higher in iNPH samples, and also ADAM10 expression was increased [64].

SFMBT1

SFMBT1 gene is placed on the region of chromosome 3p21.1 which encodes a protein consisting of 866 amino acid residues, containing 4 malignant brain tumor (MBT) repeat domains [65, 66]. The physiologic role of the SFMBT1 protein is poorly understood but relates to histone binding and it is involved in different transcription corepressor activities [65, 67]. The SFMBT1 locus is related to elevated serum urate levels, fasting glucose, and high blood pressure [68–70].

Immunohistochemical examination of the normal human brain showed that SFMBT1 protein is localized mainly in smooth muscle and endothelial cells of blood vessels, ependymal cells lining the ventricles, and epithelial cells of the choroid plexus, which plays a significant role in secretion, flow, and absorption of CSF. Therefore, it looks like that SFMBT1 gene mutations may affect the normal circulation of CSF in the brain. Patients with iNPH had SFMBT1 gene copy loss compared with

healthy controls. The copy number loss was heterozygous and occurred at the 12 kb region within intron 2 of the SFMBT1 gene [71]. There was a strong relationship between the copy number loss in SFMBT1 and iNPH leading to this idea that the copy number loss in SFMBT1 was a risk gene for iNPH [72, 73]. As the gene copy loss prevalence was similar between shunt responder and non-responder patient groups, SFMBT1 seems to be linked with enlargement of brain ventricles but not with shunt response [72].

C9ORF72

C9ORF72 gene is at 9p21.2, encoding C9ORF72 protein is found in many tissues including brain structures. Hexanucleotide repeat expansion in the C9ORF72 gene leads to behavioral variant frontotemporal dementia [74, 75], amyotrophic lateral sclerosis (as the common motor symptom in a patient with the C9ORF72 expansion), and extrapyramidal symptoms [76, 77]. Furthermore, the full or an intermediate (20–30 repeats) C9ORF72 expansion was associated with PD [78]. Atypical Parkinsonian disorders that potentially cause problems with gait could be connected to intermediate number of repeats in the C9ORF72 gene [79–83]. There was also an association between C9ORF72 expansion and iNPH and most of the carriers showed gait disabilities. Also, the mean age at onset of symptoms in patients with C9ORF72 expansion was lower than non-carriers (59 vs 70 years) [84].

APOE4

There are three different apolipoprotein E (APOE) alleles that encode three different ApoE isoproteins [85–87]. APOE4 allele is the most significant independent genetic risk factor for late-onset AD [88–90] APOE4 is also correlated with other neurological diseases [91, 92]. Studies showed that homozygous ApoE3/3 genotype was slightly associated with gait improvement in patients with iNPH but there was no other evidence for the correlation of APOE4 genotype, iNPH disease, and response to shunt [93–95].

Chromosome 19q12–13.31

Studies on five generations of a family suggested possible genetic relation between Essential tremor (ET) and Idiopathic normal pressure hydrocephalus (iNPH). This new autosomal dominant genetic disorder known as essential tremor-idiopathic normal pressure hydrocephalus (ETINPH) was detected in a family with 15 members affected with ET, of whom 3 of them in the second generation developed iNPH. Genetic analyses showed that neither of the three genes that are related to ET is involved in this family. This data raises the genetic link between iNPH and ET [96].

Several loci on chromosome 19q12–13.31, are suspected to be in association with ETINPH. Among loci in this part of the chromosome, some are more possible candidates as they are related to the nervous system functions [97]. One of these genes is the ATP1A3 which codes an isoform of the alpha subunit of N,K-ATPase which is expressed in nervous system. A mutation in the ATP1A3 gene can cause an autosomal dominant disorder called rapid-onset dystonia-parkinsonism [98]. This disease can affect patients between the ages of 15 and 45 years leading to involuntary spasms of the extremities, bradykinesia, dysarthria, dysphagia, and postural instability [99–101]. There is a chance that various mutations in the ATP1A3 gene can lead to various loss of function and various clinical manifestations from Parkinsonism to ETINPH.

Another gene is the Presenilin enhancer 2 (PSENEN) gene which encodes a protein that enhances the Presenilin production, a constituent of gamma-secretase. Gamma-secretase is one of the proteins involved in breaking down ABPP and inappropriate breaking of AMPP that leads to Alzheimer's disease [102]. Amyloid-beta A4 precursor-like protein 1 (APLP1) is structurally homologous to APP and located on chromosome 19 [103]. The list of important genes in pathophysiology of NPH is discussed in Table 2.

Conclusion

Here, we reviewed the studies that examined the biomarkers of NPH and other related neurologic disorders. There are different categories of markers such as inflammatory markers, markers related to Alzheimer's disease, and various CNS proteins. Also, the genotype results of NPH patients show that some genes in these patients have been altered, which seems to be involved in the pathophysiology of NPH and can be used as a biomarker.

Table 2 List of candidate genes involved in NPH

Gene	Relation	References
CFAP43	Nonsense gene mutation in NPH	[58]
A1R and A2AR	Low expression in NPH	[61]
Transthyretin	Low expression in NPH	[64]
AMPP	High expression in NPH	[64]
SFMBT1	Copy loss in NPH	[71–73]
C9ORF72	Full or intermediate (20–30 repeats) expansion	[84]
APOE	ApoE3/3 genotype associated with gait improvement in NPH	[93–95]
ATP1A3	Gene mutation in NPH	[99, 100]
PSENEN	Involved in AD and NPH pathophysiology	[102]
APLP1	Involved in AD and NPH pathophysiology	[103]

Differentiation of NPH from other similar neurological diseases is possible through CSF, plasma, pathology and genetic biomarkers. However, more studies are needed to provide accurate and comprehensive profiles for these diseases so that we can understand the clinical characteristics of different patients.

Abbreviations

NPH: Normal pressure hydrocephalus; iNPH: Idiopathic normal pressure hydrocephalus; CSF: Cerebrospinal fluid; AD: Alzheimer's disease; PSP: Supranuclear palsy; MS: Multiple sclerosis; Aβ: Amyloid-β; t-tau: Total tau; SAPP: Soluble amyloid-precursor proteins; NFL: Neurofilaments; NG: Neurogranin; MBP: Myelin basic protein; LRG: Leucine-rich alpha-2-glycoprotein; TGF-β1: Transforming growth factor β1; TGF βR-II: Transforming growth factor βI type II receptor; PDD: Parkinson's disease with dementia; PD: Parkinson's disease; TNF-alpha: Tumor necrosis factor-alpha; MCP-1: Monocyte chemoattractant protein 1; YKL-40: Chitinase-3-like protein-1; PTPRQ: Protein tyrosine phosphatase receptor type Q; AQ4: Aquaporin 4; CFAP43: Cilia and flagella associated with protein 43; PCD: Primary cilia dyskinesia; Ado: Adenosine; A2AR: A2A receptor; A1R: A1 receptor; PBMCs: Peripheral blood mononuclear cells; SFMBT: SFMBT1 gene; C9ORF72: C9ORF72 gene; ABPP: Amyloid protein precursor; MBT: Malignant brain tumor; APOE: Apolipoprotein E; ET: Essential tremor; ETINPH: Essential tremor-idiopathic normal pressure hydrocephalus; PSENEN: Presenilin enhancer 2; APLP1: Amyloid beta A4 precursor-like protein 1.

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FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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