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The Impact of Selected Cytokines in the Follow-Up of Normal Pressure Hydrocephalus

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Summary

Cytokines are widely known mediators of inflammation accompanying many neurodegenerative disorders including normal pressure hydrocephalus (NPH). NPH is caused by impaired cerebrospinal fluid (CSF) reabsorption and treated by surgical shunt insertion. The diagnostics is still complicated and the shunt effect is not durable; after several years, dementia may develop. In the clinical practice, biomarkers support the diagnostics as well as the further time course of many neurodegenerative diseases. Until recently, no reliable biomarker for NPH was evaluated. The attempt of this review was to make a survey concerning cytokines as possible NPH markers. Among all reviewed cytokines, the most promising are CSF IL-10 and IL-33, enabling to follow-up the disease progression and monitoring the effectiveness of the shunt insertion.

Key words

Normal pressure hydrocephalus • Cytokine • Cerebrospinal fluid • Ventriculoperitoneal shunt • Neurodegeneration

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Introduction

Cytokines are small protein molecules involved in cell signaling. They play major roles in the inflammatory processes within and outside the brain and have both beneficial and detrimental effects on the central nervous system (CNS) (Rothwell 2003). Inflammatory processes, including the cytokine action, usually contribute to disease progression (Wyss-Coray and Mucke 2002, Cunningham *et al.* 2009). The brain tissue responds to varied pathological stimuli differently than organs in the periphery. Peripheral immune cells cannot commonly penetrate into the CNS across the blood brain barrier, while in an inflammation affected brain this barrier is breached, enabling immunocompetent cells to infiltrate into the afflicted area (Lossinsky and Shivers 2004, Hampl *et al.* 2015). CNS is the most sensitive organ of the body with limited regenerative potential and rapid dissemination of inflammation (Lossinsky and Shivers 2004). Systemic and brain inflammation were reported for many neurodegenerative diseases (Alzheimer disease, Parkinson disease, multiple sclerosis), including normal pressure hydrocephalus (NPH) (Blum-Degena *et al.* 1995, Mogi *et al.* 1996, Tarkowski *et al.* 2003, Li *et al.* 2007, Seppi *et al.* 2014).

Normal pressure hydrocephalus

NPH is one of the treatable neurodegenerative diseases, affecting predominately elderly people. It is caused by altered cerebrospinal fluid (CSF) reabsorption and metabolism affecting brain homeostasis. Increased CSF volume can result in the damage of brain tissue and several brain disturbances. NPH is manifested clinically as balance impairment, urinary incontinence and dementia development (Adams *et al.* 1965, Rigamonti 2014). It is important to mention that NPH is the reason of about 5 % of all dementia cases (Relkin *et al.* 2005). The degenerative changes accompanying NPH may be reversible when they are early recognized and treated properly. The early diagnosis of NPH is difficult because

of various disease manifestations and overlap with other neurological disorders, which may also present the above-mentioned symptoms common in elderly. It could be easily mistaken for other neurodegenerative disorders, which makes NPH one of the important misdiagnosed diseases worldwide (Brean *et al.* 2009, Jaraj *et al.* 2014).

The most frequent therapeutic approach to NPH is the ventriculoperitoneal shunt insertion, connecting the brain ventricles to abdominal cavity, where the excessive CSF volume can be absorbed (Iseki *et al.* 2009, Reddy *et al.* 2014). CSF shunting can lead to partial or complete amelioration of the patient's state with full or partial return to premorbid social and health condition (Rigamonti 2014). Unfortunately the effect of the shunt is not durable. Recent data showed that nearly half of the initially well treated NPH patients eventually developed NPH-related dementia within a 4.7 years median follow-up. NPH-related degenerative changes of the brain appear usually early in the course of the disease, stressing the role of timely diagnostics (Koivisto *et al.* 2013). Diagnosis at the early stage gives patients high probability of all symptoms disappearing after shunt insertion (Kazui *et al.* 2013, Yamamoto *et al.* 2013).

NPH biomarkers

Biomarkers have been traditionally used in clinical practice to support the diagnosis, or monitor its progression by examining their levels longitudinally. Though the number of studies following the patient's outcome after the shunt insertion is increasing, no biomarker has fulfilled so far criteria required for differential diagnosis of various neurodegenerative disorders with respect on NPH (Rigamonti 2014).

CSF is the major constituent of the extracellular space in the brain. It participates in the free exchange of the most of biochemical products and therefore can better reflect the physiological or pathophysiological processes occurring in the CNS than the plasma levels (Tarnaris *et al.* 2006). For that reason, the CSF is the first biological material at stake in the search for suitable biomarkers in neurodegenerative diseases including NPH. A great advantage is the possibility to collect the CSF longitudinally after the shunt insertion.

The current search for such biomarkers is mainly focused on the proteins in the CSF (τ-protein, amyloid-β, soluble amyloid precursor protein – aAPPa, light chain neurofilament protein), especially for the differentiation of NPH and Alzheimer disease. No biomarker, however, has also brought any progress in distinguishing between NPH and Parkinson disease (Rigamonti 2014). According to their physiological and pathophysiological properties and function, cytokines may be a future promising analytes in the biomarker research.

Cytokines in NPH

In subjects suffering from NPH, several studies reporting various cytokine levels were published, predominantly in CSF. The only one study (Rota *et al.* 2006) followed up the serum levels of several cytokines in NPH subjects, but no differences in comparison with Alzheimer disease patients were found. A brief review summarizing the current knowledge concerning CSF cytokines in NPH subjects is shown in Table 1.

Pro-inflammatory cytokines – IL-1 and IL-6 family

Among all cytokines, the most discussed one in the relation to neurodegenerative disorders is IL-1. The IL-1 family is composed of its agonists, a series of protein factors, from which IL-1β plays the major role in brain neurodegeneration (Simi *et al.* 2007). This cytokine is not generally expressed or secreted under physiological conditions; its major activity seems to be limited to diseases (Dinarello and Thompson 1991). IL-1β initiates or augments multiple responses increasing the defence processes against tissue injury within as well as outside CNS. It leads to the development of inflammation following by the activation of immune cells and the formation of IL-6 (Kishimoto *et al.* 1992, Rothwell and Luheshi 2000, Janeway *et al.* 2004, Chakraborty *et al.* 2010). Thus, together with elevated CSF IL-1β in neurodegenerative diseases including NPH, elevated levels of pro-inflammatory IL-6 were also reported (Blum-Degena *et al.* 1995, Mogi *et al.* 1996, Sosvorova *et al.* 2014). Pro-inflammatory IL-6 have direct effects on both peripheral tissues and CNS, by affecting neurons and lymphocytes and inducing acute phase protein synthesis (Kishimoto *et al.* 1992, Janeway *et al.* 2004). Together with elevated IL-1β, the elevated CSF IL-6 levels were reported in neurodegenerative diseases such as Alzheimer and Parkinson disease (Blum-Degena *et al.* 1995, Mogi *et al.* 1996), as well as in subjects suffering from subarachnoid hemorrhage, schizophrenia and depressive disorders (Mathiesen *et al.* 1993, Sasayama *et al.* 2013). Both cytokines also participate in the NPH

development (Sosvorova *et al.* 2014).

One of the recently discovered IL-1 family members is IL-33. It is expressed after pro-inflammatory stimulation by many cell types, especially in the brain and spinal cord and it is also thought to be released on cell lysis (Schmitz *et al.* 2005, Liew *et al.* 2010). IL-33 can induce the proliferation of brain microglia and also enhance IL-1β expression. At the same time it also induces the expression of anti-inflammatory IL-10 (see below).

Table 1. Altered cerebrospinal fluid cytokines in various types of adult hydrocephalus.

Cytokine	Studied group	Main findings	Reference
IL-1β	NPH, Alzheimer disease	Lower in NPH compared to Alzheimer disease	(Cacabelos *et al.* 1991)
IL-6	Various types of adult hydrocephalus	Increased in hydrocephalus following hemorrhage and embolization of unrupted intracranial aneurysms compared to normal controls	(Killer *et al.* 2010)
IL-8	Various types of adult hydrocephalus	Increased in hydrocephalus following hemorrhage compared to normal controls	(Killer *et al.* 2010)
	NPH	Increased after ventriculostomy compared to the samples collected before the procedure	(Pyykko *et al.* 2014)
TGF-β	NPH	Elevated in NPH compared to controls without neurological diseases	(Li *et al.* 2007)
	NPH, Alzheimer disease	Lower in NPH compared to Alzheimer disease	(Rota *et al.* 2006)
	Communicating hydrocephalus after subarachnoid hemorrhage (SAH)	Higher in communicating hydrocephalus after SAH compared to controls without hydrocephalus	(Kitazawa and Tada 1994)
TNFα	NPH	Lower in NPH compared to controls without hydrocephalus	(Leinonen *et al.* 2011)
	NPH	Increased in NPH, reversed following shunt implantation in parallel with the clinical improvement, compared to the controls	(Tarkowski *et al.* 2003)

Pro-inflammatory cytokines – IL-17 family

The IL-17 family is a heterogeneous group, including both pro-inflammatory (IL-17A and IL-17F) and anti-inflammatory cytokines (IL-17E is also known as IL-25). Among all, the biological functions of IL-17A and IL-17F are best understood. These two cytokines are known to mediate proinflammatory responses, with certain differences depending on the type and site of inflammation (Ishigame *et al.* 2009, Jin and Dong 2013). They are produced by specialized T cells, called Th17 cells involved in the adaptive immunity. IL-17A, as other pro-inflammatory cytokines, induces the production of IL-1β, IL-6 and TNF-α (Jovanovic *et al.* 1998, Witowski *et al.* 2004). Uncontrolled production of IL-17A can result in excessive pro-inflammatory cytokine expression and chronic inflammation leading to tissue damage and autoimmunity. All IL-17 family cytokines are associated with several autoimmune diseases, including multiple sclerosis and rheumatoid arthritis (Ishizu *et al.* 2005, Jin and Dong 2013). Cytokines produced by Th17 cells are the main power that manage the CNS inflammation and formation of lesions (Park *et al.* 2005). The overproduction of IL-17A may deteriorate the inflammatory reactions and contribute to tissue injury.

Anti-inflammatory cytokines

Anti-inflammatory interleukines play opposite functions to the pro-inflammatory ones. Among them the effect of IL-4 and IL-10 is the best understood. Generally, they can suppress pro-inflammatory cytokine production and action, subsequently protecting the brain from excessive immune reaction (Hart *et al.* 1989, Park *et al.*

2007, Rubio-Perez and Morillas-Ruiz 2012). IL-4 is thus a significant player in the regulation of brain immunity, with consequences for neurological and neurodegenerative disorders (Gadani *et al.* 2012, Sosvorova *et al.* 2014).

Another anti-inflammatory cytokine, IL-10, is also involved in the pathophysiology of CNS disorders. It inhibits the production of reactive oxygen intermediates (Krakauer 1995) and is considered to be an efficient modulator of glial activation, maintaining a balance between pro- and anti-inflammatory cytokines in the CNS (Sawada *et al.* 1999, Qian *et al.* 2006, Park *et al.* 2007). A neuroprotective effect of IL-10 was reported in Parkinson disease (Qian *et al.* 2006), lower levels of CSF IL-10 were found in patients with Alzheimer disease (Remarque *et al.* 2001), contrasting with previously published elevated levels in NPH (Sosvorova *et al.* 2014). Our observation shows IL-10 as an analyte having potential in the differential diagnosis of the latter two diseases.

The follow-up of cytokines in CSF and plasma after shunt insertion

As described above, the only differences in cytokine composition between NPH subjects and controls were found in CSF. In our previous study (Sosvorova *et al.* 2014), the levels of IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, INF-γ, soluble CD40 ligand (sCD40L) and TNF-α in CSF from patients diagnosed with NPH were investigated and compared to the controls. Increased CSF levels of IL-1β and IL-6 in NPH were found, reflecting the inflammatory changes in the brain. Their levels decreased during the lumbar drainage. It can be explained by activation of defense mechanisms suppressing the detrimental process in the brain. No changes were observed in plasma.

The same patient group (Sosvorova *et al.* 2014) was further followed-up for 2 years from the shunt insertion, in order to evaluate possible prognostic laboratory markers of the patients' outcome. As shown in Figure 1, the CSF pro-inflammatory cytokines IL-1β and IL-6 decreased after shunt insertion, reflecting the inflammatory changes in the NPH brain and the amelioration of the patient's state after shunt insertion. The constant CSF IL-1β and IL-6 levels within 2 years after shunt insertion confirm the durable positive effect of shunt insertion. The time course of CSF anti-inflammatory IL-4 coincides with the elevation of the abovementioned cytokines.

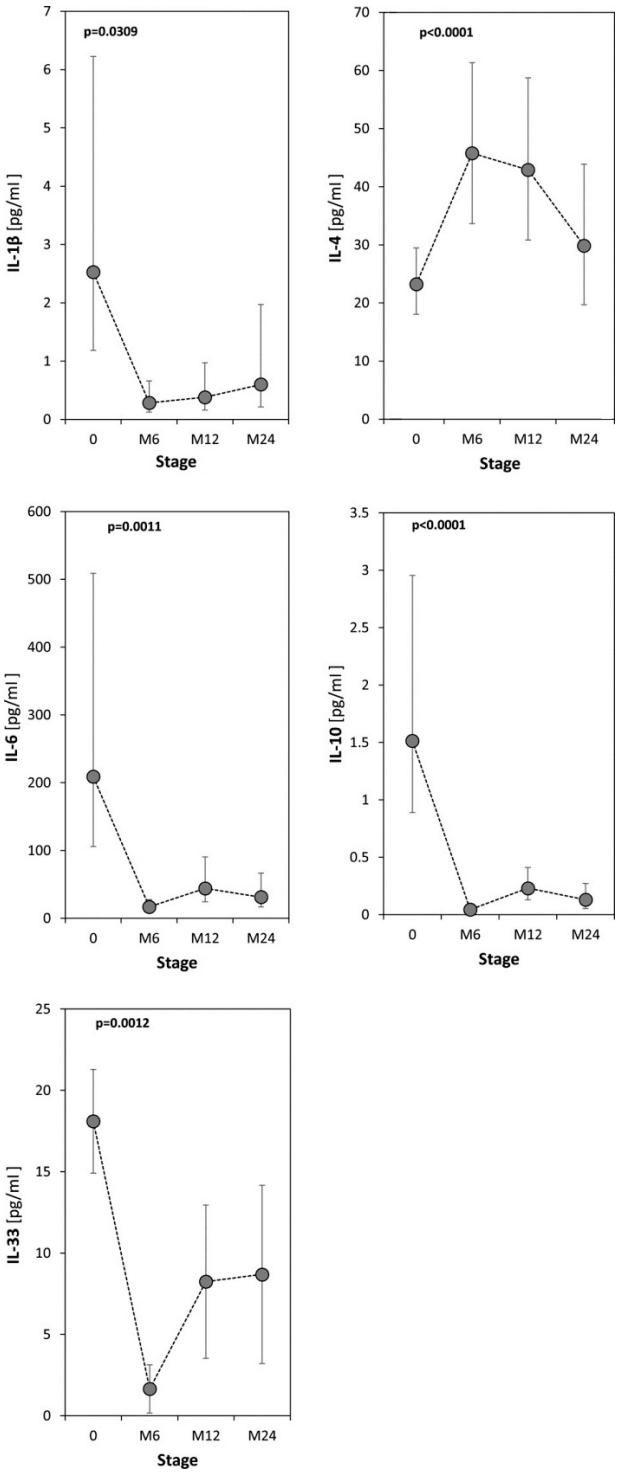

Fig. 1. The significantly changed cerebrospinal fluid (CSF) cytokine levels in subjects with diagnosed normal pressure hydrocephalus, who underwent ventriculoperitoneal shunt implantation. The stage indicates the period when CSF was collected: 0 means the period when the disease was diagnosed; M6 means the period within 6 months from the shunt insertion; M12 means the period within 12 months from the shunt insertion; M24 means the period within 24 months from the shunt insertion. The statistical significances between stages are indicated above each graph. The stages differ significantly, when the confidence intervals do not overlap. The statistics was performed using repeated measures of the ANOVA model followed by least significant difference (LSD) multiple comparisons.

The elevated CSF IL-10 levels in NPH were found in our previous study (Sosvorova *et al.* 2014), the two-years follow-up showed that the CSF IL-10 as well as IL-33 significantly decreased after 6 months from shunt insertion. After 12 months their levels increased again, but did not reach the levels before shunt insertion and remained stable within 24 months. Considering the time-related CSF IL-33 changes, this pro-inflammatory cytokine appear as possible marker for the follow of the development and progression of NPH. The prompt decrease of its levels in CSF reflected the rapid patient's amelioration after shunt insertion. Concerning CSF IL-10, its decrease after shunt insertion and its stabilization at levels lower than 0.5 pg/ml for 2 years makes CSF IL-10 possible diagnostic tool in the follow-up to the patient's outcome after shunt insertion.

It is also worth mentioning that no significant changes of IL-17A and IL-17F CSF levels were observed during the 2-years monitoring period. It shows, that they are not suitable indicators of the disease progress. The same situation concerns pro-inflammatory IL-21, IL-22, IL-23, IL-31, TNF-α and INF-γ.

Conclusion

In this review we summarized the current knowledge concerning the role of pro- and anti-inflammatory cytokines in the NPH with respect to the assessment of their possible role in the early diagnostics as well as for the follow-up of the disease's progress. This review is supplemented by our exposure on the follow-up of selected cytokine changes. The most promising cytokines are CSF IL-10 and IL-33, applicable in NPH diagnosis as well as in the observation of effectiveness of the shunt insertion. In the subsequent study, we will evaluate the clinical significance of above mentioned cytokines.

Conflict of Interest

There is no conflict of interest.

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