Inflammation and Sepsis **Edited by: P. Fraunberger**

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Diagnostic relevance of CSF interleukin-6

DOI 10.1515/labmed-2015-0111
Received October 5, 2015; accepted October 20, 2015

Abstract: In 1985 interleukin 6 (IL-6) was first identified as a differentiation factor for B-cells (B-cell stimulatory factor 2) which caused B-cells to mature and produce antibodies. Numerous studies now demonstrate the pleiotropic character of IL-6, which has been shown to possess important functions in the immune system, the regulation of hematopoesis, inflammation and oncogenesis. In the central nervous system (CNS), IL-6 is involved in neurogenesis and the response of neurons and glia-cells to various injuries. CNS infections, cerebral ischaemia, CNS traumata or chronic inflammatory diseases with CNS manifestations such as neuro-lupus or neuro-sarcoidosis are associated with increased IL-6 levels in the cerebrospinal fluid (CSF). Thus, the use of IL-6 as a diagnostic and prognostic tool in these diseases is being investigated. In this review we aim to provide an overview of current studies and evaluate the diagnostic significance of CSF-IL-6.

Keywords: cerebral ischaemia; CSF-IL-6; diagnostic relevance; encephalitis; meningitis; multiple sclerosis; systemic lupus erythematodes; traumatic brain injury.

Interleukin 6 – classification, structure, signaling cascade

Interleukin 6 is a cytokine of a pleiotropic nature, which was first identified as a differentiation factor for B-cells almost 30 years ago. It was then shown that the hybridoma/plasmocytoma growth factor, which triggered the polyclonal growth of plasma cells in the spleen and lymph nodes in animal studies, was identical to IL-6. Through the use of monoclonal antibodies against IL-6 and recombinant IL-6, it was further discovered that the proteins IFN-β2, 26 kDa protein and the hepatocyte-stimulating factor were also IL-6 [1].

According to modern classification, IL-6 is part of the subgroup of interleukin-6-type cytokines. Apart from IL-6, this group also comprises the cytokines interleukin 11 (IL-11), the leukemia-inhibitory factor (LIF), oncostatin M (OSM), the ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1) and cardiotrophin-like cytokine (CLC). All cytokines in this subgroup have in their molecular structure four long alpha helices, called A, B, C and D [2] – see Figure 1.

Receptors for interleukin-6-type cytokines can be divided into non-signal-transmitting α-receptor proteins (Class I cytokine receptors) without intrinsic enzymatic activity, such as IL-6Rα for IL-6, and signal-transmitting receptor proteins (gp130, LIFR and OSMR). In the case of IL-6, a hexamer consists of two IL-6 molecules, two IL-6R and a gp130 homodimer.

Among the IL-6-type cytokines, signals are transmitted only for IL-6 and IL-11 via gp130 homodimers. The other cytokines in this group interact via heterodimers that consist of gp130 and LIFR (such as LIF and CNTF) or of gp130 and OSMR (OSM) [2]. The joint receptor subunit gp130 could be responsible, at least in part, for the redundancy of the cytokine effects in this subgroup [3]. While gp130 is expressed ubiquitously, the expression of the α-receptor subunits (IL-6Rα, etc.) is strictly limited, which also limits the number of cells that can react to an IL-6-type cytokine. However, it has been shown that soluble IL-6R (sIL-6R), when combined with IL-6, can activate cells that themselves express only gp130 – a process also known as “trans-signaling”. Soluble IL-6R is formed under physiological conditions either through limited proteolysis of the extracellular domain of membrane-bound IL-6R via metalloproteinases, such as ADAM10, or through alternative splicing of IL-6mRNA. In addition to the soluble form of IL-6R, there is also a soluble variant of gp130 (sgp130), which can inhibit trans-signaling [3].

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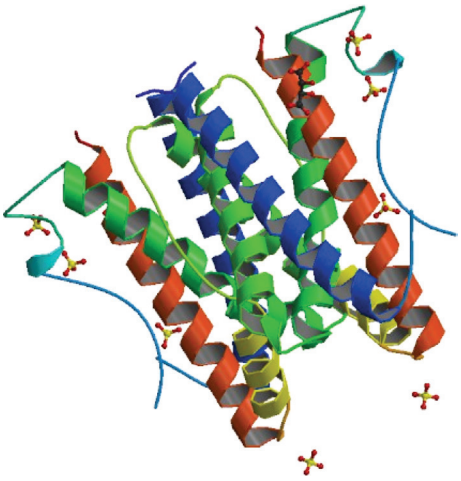

Figure 1: Structure of human interleukin 6.
(Image from the RCSB PDB (www.rcsb.org) of PDB ID: 1ALU (Somers WS, Stahl M, Seehra JS. A crystal structure of interleukin 6: implications for a novel mode of receptor dimerization and signaling. EMBO J 1997;16: 989–97)).

Signal transduction via membrane-bound IL-6R or trans-signaling via sIL-6R causes the activation of intracellular tyrosine kinases, particularly Janus kinase (JAK) – see Figure 2. This, then, activates a series of further proteins, such as the STAT (signal transducer and activator of transcription) family of transcription factors, the RAS-RAF-MAPK signal pathway or phosphatidylinositol 3 (PI3) kinase [2, 3].

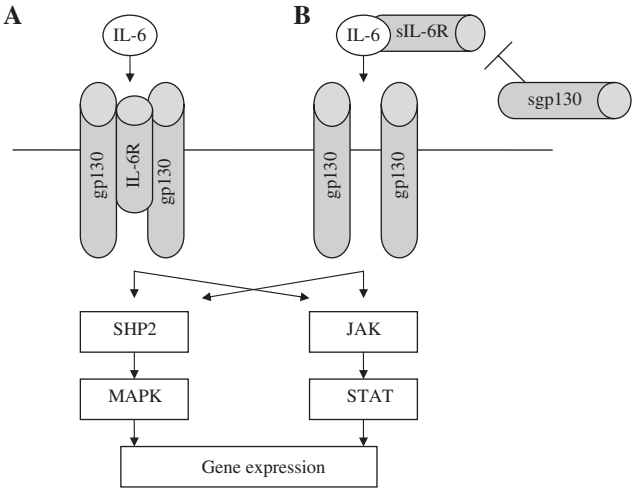

Figure 2: IL-6 signal transduction via (A) activation of the membrane-bound IL-6 receptor (IL-6R) and (B) via trans-signaling through the soluble IL-6 receptor (sIL-6R) and membrane-bound gp130, which is expressed ubiquitously.
The soluble form of gp130 (sgp130) can inhibit trans-signaling. Signal transduction leads to the activation of the JAK/STAT and MAPK cascades.

Expression in CNS, induction by infection or injury

In the CNS, IL-6 and IL-6R are primarily synthesized and/or expressed by glial cells – particularly by astrocytes and microglia – as well as by neuronal cells [3–9].

Another important producer of IL-6 in the CNS are endothelial cells, which can secrete large amounts of IL-6 when stimulated with LPS, for example [10, 11]. As for the peripheral nervous system, studies on rats have shown that IL-6 and IL-6R are expressed by sympathetic and sensory ganglia, as well as by adrenal chromaffin cells [12, 13].

The IL-6 synthesis in the CNS is regulated by means of a series of different cytokines and neurotransmitters. Both IL-1β and TNFα are inducers of IL-6 in astroyctes [9, 14], with IL-1β showing a stronger effect on astrocytes of human embryos than TNFα [14].

In addition, the synthesis of IL-6 mRNA was confirmed in human fetal microglia [15] as a result of stimulation with IL-1β, as well as in murine cortical neurons [16]. Furthermore, production of IL-6 by microglia can also be induced by interleukin 13 and interleukin 4, with IL-6 synthesis being increased when combined with IL-1β [17]. Using human astrocyte cell lines, substance P, histamine [18–20] and the prostaglandins E1 and E2 (but not the prostaglandins D2 and F2 [21]) have been shown to also induce the synthesis of IL-6. The induction of IL-6 by IL-1β in astrocytes requires the transcription factor nuclear factor-kappaB (NFkappaB), whereas the induction of IL-6 by substance P and histamine involves the nuclear factor-IL-6 (NF-IL-6) [20]. Histamine and substance P increase the production of inositol phosphates and raise intracellular Ca levels, which might point to an involvement of the phosphatidylinositol biphosphate/proteinkinase C signaling path [19].

Apart from induction by cytokines, the synthesis of IL-6 in microglia can also be stimulated directly by bacterial components, such as lipopolysaccharides (LPS) [9, 15]. In rats injected with LPS, IL-6 mRNA was produced in the choroid plexus and circumventricular organs (CVO), such as the subfornical organ and the area postrema. LPS also induced the synthesis of IL-6R in the central nucleus of the amygdala, the hippocampus, the paraventricular nucleus of the hypothalamus, the cerebral cortex and in blood vessels. The expression of gp130 mRNA was elevated in the CVO and in the endothelium of the brain capillaries [22].

Animal experiments have shown that both virus-infected astrocytes and microglia secrete IL-6 [23].

Mechanical damage to human astrocyte cell cultures also resulted in significantly increased IL-6 levels in the supernatant within 2 h of the trauma [24]. Interleukin-6 mRNA was detected in large and medium-sized neurons by means of in-situ hybridization, following axotomy of the sciatic nerve in rats [25]. The cerebrospinal fluid of rats exhibited elevated IL-6 levels within 1 h of a mechanical injury. The maximum levels were reached between two and 4 h following the trauma. After 24 h, the concentration levels returned to the baseline [26]. Concurrent to the increase of IL-6 after trauma, IL-6R expression in the brain of rats was also found to be elevated, and this effect was not limited to the injured area [27]. Focal cerebral ischemia in an animal model led to an increased expression of IL-6 mRNA, but without affecting the transcription of the receptors IL-6R and gp130 [28]. Likewise, hypoxia induced the secretion of IL-6 by cerebral endothelial cells [11].

Meningitis/encephalitis

Elevated IL-6 levels were reported in the cerebrospinal fluid of patients with bacterial meningitis as early as 1988 [29]. While patients with septic shock exhibited elevated IL-6 levels without any statistically significant difference between serum and CSF, patients with bacterial meningitis, despite a compromised blood-brain barrier, had significantly higher IL-6 levels in the CSF than in the serum (IL-6 CSF median 150 ng/mL, IL-6 serum median 0.3 ng/mL, $p<0.0001$) [30, 31].

Both cell count and protein concentrations correlated with IL-6 levels in the CSF of patients with bacterial meningitis [29, 30]. No correlations were found between CSF IL-6 and immunoglobulin indices [29].

The highest IL-6 levels in connection with bacterial meningitis were observed within the first 5 days of the disease [29]. In animals, elevated IL-6 levels were already present 3 h after an injection with bacterial LPS and/or viable meningococci. In contrast, infiltration with granulocytes only started 4 h after the injection of the pathogens [30].

Patients with a ventriculostomy-associated infection exhibited significantly elevated intrathecal IL-6 levels 1 day before changes of the traditional infection parameters CSF cell count and total protein were registered and before clinical changes occurred. With a cutoff of >2700 pg/mL (corresponds to 4050 pg/mL under WHO standards), a 6.09 times higher risk (95% CI: 2.62–14.18%) for the presence of a ventriculostomy-associated infection was calculated on the day of diagnosis using conventional criteria. The predictive value was at 89% (95% CI: 79.6–98.0%); sensitivity at 73.7% and specificity at 91.4% [32].

Among the cytokine concentrations of IL-6, TNFα and IL-1β in the CSF of patients with a ventriculoperitoneal shunt, IL-6 provided the highest diagnostic relevance for the diagnosis of a shunt infection with a sensitivity of 80% and a specificity of 98% [33]. In patients following a subarachnoid hemorrhage and with subsequent ventriculostomy, measured IL-6 levels were ten to a thousand times higher in the CSF than in the plasma. CSF concentrations above 10,000 pg/mL were linked to a ventriculostomy-associated infection [34]. Among patients with suspected meningitis, the average CSF IL-6 level in the group of confirmed bacterial meningitis was at 1495 (95% CI: 371.7–2618.6), whereas the average concentration for patients without bacterial meningitis was 7.34 (95% CI: 3.94–10.73) [35]. In another study using a cutoff of 644 pg/mL, a sensitivity of 92.3% and a specificity of 89.5% with an AUC of 0.962 were achieved for the diagnosis of bacterial meningitis [36].

The use of IL-6 CSF levels to differentiate between aseptic and bacterial meningitis has been assessed controversially in the literature. Hsieh et al. found significantly higher CSF IL-6 levels in patients with bacterial meningitis than in those with aseptic meningitis. However, it must be noted that the stated specificity was only 51%, with a sensitivity of 96% [37]. A significant difference ($p<0.001$) in CSF IL-6 levels was also found in children suffering from aseptic or bacterial meningitis [38]. Another group examining neurosurgical patients, however, was unable to define a sufficiently sensitive and specific cutoff for CSF IL-6 to differentiate between aseptic CSF pleocytosis and an infection, despite significantly increased CSF IL-6 levels in connection with a bacterial infection [39]. Even in patients suspected of meningitis with significantly elevated CSF IL-6 levels measured, no significant difference between aseptic and bacterial meningitis was found [40].

Regarding the prognostic relevance of CSF IL-6, it has been shown that patients with bacterial meningoencephalitis in poor clinical condition exhibit higher CSF IL-6 levels than patients with a moderate or mild clinical course. The CSF IL-6 levels dropped over time in patients who recovered, while only minor reductions were detected in patients with a fatal outcome [41]. In contrast, high CSF IL-6 levels in patients with bacterial meningitis were associated with worse neurological outcomes (OR 0.18; 95% CI 0.05–0.69; $p=0.013$) [36]. On the other hand, a rapid drop in CSF IL-6 levels in patients with an invasive meningococcal infection was associated with a severe course of the disease [42].

Furthermore, using serial CSF IL-6 analyses it was possible to monitor the treatment of a premature infant with shunt-associated, methicillin-resistant staphylococcus aureus ventriculitis [43].

Compared to bacterial meningitis, patients with viral meningitis tend to exhibit lower CSF IL-6 levels [29, 44, 45]. Taskin et al., conducting a study on children suffering from meningitis, were able to show, at the time of diagnosis, a significant difference between the group with bacterial meningitis (mean±standard deviation: 349.3±169.2 pg/mL) and the group with viral meningitis (168.1±143.8 pg/mL) ($p<0.05$). Forty-eight to 72 h after commencing treatment, the group with bacterial meningitis (234.0±195.0 pg/mL) continued to exhibit significantly higher CSF IL-6 levels than the group with viral meningitis (108.0±75.2 pg/mL) ($p<0.001$) [44]. A study involving 81 children also determined significant differences ($p<0.001$) between the CSF IL-6 levels for bacterial meningitis (mean 180.74) and those for viral meningitis (mean 39.08) [38].

Another study group observed a sensitivity of 80.7% and a specificity of only 53.3% with respect to the differentiation between bacterial (652±287 pg/mL) and viral meningitis (282±161 pg/mL) in children [45].

As is the case with bacterial meningitis, the highest levels with viral meningitis are observed during the first days of the disease [29]. The CSF IL-6 levels also correlate with the cell count and protein concentration in the case of viral meningitis [29].

Patients with herpes simplex encephalitis (HSE) had significantly higher levels than a control group, and IL-6 levels correlated with the severity of the disease [46, 47]. For instance, CSF IL-6 levels of patients needing artificial respiration were significantly higher ($p=0.023$). Similar results were found in patients with changes in the CT who were undergoing mechanical ventilation ($p<0.001$). The combination of neurological complications and CT changes compared to the control group was at $p\leq0.05$, at the borderline of statistical significance. With a cutoff of 983.34 pg/mL, the sensitivity for the occurrence of neurological complications was 66.7%, and the specificity 79.3% (AUC 0.756; $p=0.012$). CSF IL-6 levels further correlated with the death of patients. Using a cutoff of 1092.81 pg/mL (AUC 0.794; $p=0.025$) sensitivity was determined at 75.0% and specificity at 83.9%. In contrast to these results, the analysis of serum IL-6 was not useful to assess the course of HSE [46]. Significantly elevated CSF IL-6 levels were also found in children with acute herpes zoster meningitis [48], in advanced stages of an HIV infection [49] and in connection with norovirus encephalopathy [50].

In the course of the antiretroviral treatment of an advanced HIV infection, an immune reconstitution inflammatory syndrome (IRIS) occurs in 20%–40% of patients with cryptococcal meningitis who have not been treated at that point. Patients who developed IRIS exhibited lower CSF IL-6 levels at the time they were diagnosed with cryptococcal meningitis than patients who did not develop IRIS. The lower inflammation levels in the CSF of patients who did not develop IRIS might be due to an existing ineffective immune response, which contributes to the development of IRIS over the course of the antiretroviral treatment. In patients who were thought to have IRIS, it was possible to differentiate between IRIS and the recurrence of cryptococcal meningitis by means of cytokine profiles containing CSF IL-6 [51].

Further potential areas of application

In line with the different inducers of IL-6 synthesis and secretion, elevated IL-6 levels were not only detected in connection with infectious diseases of the CNS, but also in the course of trauma, insult or inflammatory autoimmune diseases like multiple sclerosis (MS) or systemic lupus erythematosus (SLE).

Multiple sclerosis

Multiple sclerosis is a chronic, inflammatory, demyelinating autoimmune disease of the CNS with heterogeneous clinical presentation, characterized usually by a progression in episodes. IL-6 was already detected in the acute and chronically acute plaques of MS patients back in 1997, mostly associated with glial cells that occur more frequently at sites with active demyelination and immune activation [52]. It was shown further, in an animal model, that IL-6-deficient mice were resistant to a demyelinating form of experimental autoimmune encephalomyelitis [53].

Despite the findings from animal models, the relevance of CSF IL-6, sIL6R gp80 and sgp130 to the diagnosis and/or ongoing assessment of MS is seen as controversial [54–58]. This may be due to the fact that while IL-6 does have pathophysiological relevance, in the plaques, the cytokine is not secreted into the CSF in significant quantities [59].

No association has been found either between IL-6 and/or sIL-6R levels in the serum and/or CSF on the one hand, and anti-myelin oligodendrocyte glycoprotein

antibodies on the other – the latter are involved in the autoantibody-mediated demyelination and, thus possibly, in the development of lesions [56].

Nor has any association with the progression of MS been found for various IL-6 polymorphisms, despite effects on IL-6 activity and/or expression [60, 61]. One meta-analysis showed that Asians with the IL-6-174G/C polymorphism had a slightly elevated risk of developing MS. But this association has not been confirmed in the overall population or in the Caucasian population [62].

A possible benefit of measuring CSF IL-6 might lie in the differential diagnosis with respect to other neurological diseases that can present symptoms similar to MS. In contrast to MS, elevated CSF IL-6 levels were found, for example, in connection with neuroborreliosis, neurosarcoidosis, Wegener's granulomatosis, and CNS lupus. Thus, elevated CSF IL-6 levels in a patient suspected of MS could point to a different underlying disease [59].

Systemic lupus erythematosus

Systemic lupus erythematosus is a chronic inflammatory autoimmune disease with vasculitis or perivasculitis of the small arteries and arterioles, involving multiple organs. Neurological changes (neuro-lupus), together with renal involvement, are key to prognosis and can manifest, for example, as vigilance deficits, depression, insults or MS-like symptoms.

Given the varied clinical manifestations, neuro-lupus is a possible candidate for the differential diagnosis of a series of different neuropsychiatric conditions, from which it is often difficult to differentiate [63].

Unlike SLE patients without CNS manifestations, patients with neurological involvement have shown elevated CSF IL-6 levels. As such, the elevated IL-6 levels did not correlate with the CSF/serum albumin quotient, a measure for the functional impairment of the blood-brain barrier. After the neurological manifestations subsided following therapeutic intervention, the CSF IL-6 levels dropped significantly, which suggests it might be a useful factor for assessing disease activity [64]. Tsai et al. described significant differences between moderately elevated CSF IL-6 levels in neuro-lupus patients (71.40±5.89 pg/mL), strongly elevated CSF IL-6 levels in connection with a CNS infection (374.24±92.61 pg/mL), slightly elevated concentrations for other inflammatory, neurological conditions (33.92±29.36 pg/mL), and controls without inflammatory CNS disease (4.35±3.00 pg/mL) [65]. Patients suffering headaches in connection with neuropsychiatric SLE exhibited elevated CSF IL-6 levels compared to SLE patients without neurological changes ($p<0.004$), as well as compared to patients without autoimmune diseases ($p<0.001$). For the diagnosis of a lupus-psychosis, a sensitivity of 87.5% and a specificity of 92.3% were achieved with a cutoff of 4.3 pg/mL, with the caveat that infectious meningoencephalitis and accidents affecting the cerebrovascular system were excluded [66]. At the same time, SLE patients in an acute confusional state (ACS) exhibited significantly higher CSF IL-6 levels than the group without CNS involvement ($p<0.05$) [67].

Despite a series of studies that found significantly elevated CSF IL-6 levels in SLE patients with neurological involvement [68–71], another study did not find any significant difference between patients with headaches due to neuro-lupus and those with other neuropsychiatric changes [72].

The results of patients with unselected neuropsychiatric SLE manifestations exhibited an increase in CSF IL-6 only in three out of 26 cases. These cases did not correlate with clinical symptoms, which the authors attribute to the heterogeneity of the pathogenesis of neuropsychiatric SLE [73].

A meta-analysis to study the relevance of IL-6 polymorphisms points to a significant association between IL-6-174G/C polymorphism and SLE risk in the overall population based on a recessive model and/or allele analysis. In addition, this polymorphism was associated with discoid skin lesions. Using the recessive model, a significant association with SLE risk was also found for the IL-6-572G/C polymorphism, but not by means of a dominant model and allele analysis [74].

Traumatic brain injury

Patients with severe traumatic brain injury (TBI) show a pronounced acute phase reaction. CSF IL-6 concentrations in patients with isolated TBI reached significantly higher levels (maximum of 31,000 pg/mL) than in serum (up to 1100 pg/mL). In the first phase following the trauma, a correlation between IL-6 in CSF and in serum was found ($p=0.001$), in accordance with a severe dysfunction of the blood-brain barrier [75].

Animal models have shown that IL-6 knock-out mice exhibit a limited inflammatory response, elevated oxidative stress, inhibited neuroglial activation, reduced lymphocyte recruitment and poorer healing rates. By contrast, faster healing rates were observed in GFAP-IL-6 mice with increased IL-6 expression in the CNS following a TBI – thanks to improved revascularization [3].

Although CSF IL-6 is known to be an important factor in the inflammatory response following a TBI, studies so far

have not been able to work out a clear connection between CSF IL-6 and the patient's prognosis. Some studies postulate that elevated CSF IL-6 levels are associated with an improved clinical outcome [76–78] – based on correlations between peak levels and outcome in accordance with the Glasgow Outcome Scale (GOS) 3 months [76] or 6 months [77] after the trauma. In one study, the relevant measurements were not taken from the CSF, but from intracranial microdialysate from the patient's parenchyma [77]. No correlation between CSF IL-6 and the severity of the trauma was detected in the initial assessment of patients under the Glasgow Coma Scale [78].

A correlation between CSF IL-6 and poor outcome after a TBI has been described in other studies. Chiaretti et al. compared CSF IL-6 levels two and/or 24 h after a trauma, and the increase correlated with the severity of the trauma according to the Glasgow Coma Scale and poor clinical outcome [79].

In a recent study using serial CSF IL-6 measurements in the first 5 days following a trauma, two different acute-CSF IL-6 profiles were worked out, with the result that higher-profile patients achieved worse GOS results after 6 months [80]. What was striking in this case was that the lower group exhibited a drop in CSF IL-6 levels from day 3 to day 5, which was not the case for the higher group. Thus, the poorer prognosis of patients with a higher CSF IL-6 profile could be due to the persistent elevation of CSF IL-6 [80].

Differing data exists on the potential association between IL-6 polymorphisms and the prognosis for TBI patients. An association between the IL-6 polymorphism 174C/G and the patient's survival was observed in patients with a severe TBI – the GG genotype was detected significantly more frequently in the group of patients who survived than in the group of those who died [81]. By contrast, another study of patients with polytrauma did not find any statistically relevant difference in the clinical outcome with respect to the 174G/C polymorphism. For the 596G/A polymorphism as well, no statistically significant differences in the patients' survival were found for heterozygous or homozygous polymorphism when compared to controls [82].

Ischemic stroke

A number of proinflammatory cytokines, including IL-6, are released due to cerebral ischemia. The initial increase in CSF IL-6 correlates positively with the size of the brain lesion in stroke [83–88], as well as with the clinical outcome 1 week [87, 88] or 1 month [88] after the stroke. Thus, CSF IL-6 allows for a prognostic assessment of the patient even before the extent of the stroke can be determined by radiological methods [83].

Cerebral ischemia also causes elevated CSF IL-6 levels in mature newborns with asphyxia, with the concentrations in this case being significantly higher than those measured in septic newborns [89].

The clinical relevance of the 174G/C-IL-6 polymorphism in connection with ischemic stroke is controversial, according to the current literature. While some studies describe a connection between the C-allele and the CC genotype, others have found an association with the G-allele or GG genotype, or no association with ischemic stroke at all [90].

Also controversial is the connection between the 174G/C polymorphism and the occurrence and/or clinical outcome of an ischemic stroke in pediatric patients [91, 92]. A recent meta-analysis on 30 studies did not find any significant association between the IL-6 polymorphisms 174G/C or 572G/C and ischemic stroke [93]. This finding is confirmed by another meta-analysis that did not discover any association between the IL-6 polymorphism and stroke risk either [94]. The differences in the findings of the individual studies could be due to the complex IL-6 physiology, differences in the subpopulations examined, as well as differences in the statistical significance of the studies [90, 93].

Summary

Elevated CSF IL-6 levels occur in connection with a series of different CNS diseases due to the induction of IL-6 by various types of injury, such as inflammatory stimuli, mechanical injury or cerebral ischemia.

Patients with bacterial CNS infections exhibit the highest CSF IL-6 levels in the initial days of the disease. According to one study, CSF IL-6 levels were significantly elevated 1 day prior to an increase in the traditional infection parameters, such as CSF cell count and total protein. These findings imply a high potential benefit for early diagnosis of bacterial CNS infections and thus for rapid initiation of treatment, but will have to be confirmed by further studies. The increase of CSF IL-6 after neurosurgery or traumatic brain injury could complicate the diagnosis of an additional infection in the case of a one-time analysis of CSF IL-6 and may therefore require serial measurements in order to assess possible trends in these patients. Furthermore, serial measurements could serve as treatment monitoring, indicating any necessary adjustments to the regimen of antibiotics.

Another potential benefit can be found in the quick evaluation of the prognosis and severity of the infection.

Regarding viral CNS infections, lower IL-6 levels tend to be measured than is the case with bacterial meningitis or encephalitis. The highest concentration levels are observed in the initial days of illness, which is comparable to bacterial infections.

The CSF IL-6 analysis could be used as a further tool in the differentiation between bacterial and viral etiology until the pathogen has been identified. Even though various studies have observed significant differences in CSF IL-6 levels between patients with bacterial and viral CNS infections, or between the presence and absence of infection, having further studies with a high statistical significance to work out specific cutoffs would be desirable.

As for herpes simplex encephalitis, a correlation between the CSF-IL6 levels and the progression of the disease up to the death of the patient has been established. To what extent CSF IL-6 can be used for the follow-up assessment of viral encephalitis of a different etiology is a question that must be addressed by further studies.

Despite the detection of IL-6 in acute and chronically active plaques of MS patients, the relevance of CSF IL-6 may be limited with respect to the diagnosis and/or follow-up assessment of MS, possibly due to insufficient secretion into the CSF. One potential benefit here might only lie in the differentiation from other diseases that present with similar symptoms but are accompanied by elevated CSF IL-6.

Studies on SLE patients with neuro-lupus point to a possible application of CSF IL-6 as a diagnostic tool, particularly for the purpose of differentiating from other neuropsychiatric conditions as well as of assessing disease activity. However, it should be mentioned that not all neuropsychiatric symptoms in SLE are accompanied by elevated CSF IL-6 levels. Further studies would be required to assess the sensitivity and specificity of CSF IL-6 with regard to SLE.

As for the prognostic value of CSF IL-6 in TBI patients, studies have produced partially contradictory findings. While some studies conclude that high CSF IL-6 peak levels are associated with a better outcome, others have found a correlation between high CSF IL-6 levels and poor prognosis.

A possible explanation of this discrepancy is that the short-term up-regulation has a favorable effect on the outcome of the illness by way of a neuroprotective response, while persistent CSF IL-6 increases are linked to a poorer outcome, in line with a protracted inflammatory response. A drop in CSF IL-6 levels from day 3 to day 5 following TBI has been associated with a favorable prognosis, and might be indicative of the inflammatory

Table 1: Overview of possible application areas for CSF IL-6.

Disease	Application of CSF IL-6	Assessment	References
CNS infection, bacterial	Diagnosis	++	[29–36]
	DD, aseptic/bacterial	−/+	[37–40]
	Prognosis	++	[36, 41, 42]
	Therapy monitoring	+	[43]
CNS infection, viral	Diagnosis	+	[29, 46–50]
	DD, bacterial/viral	+	[29, 38, 44, 45]
	Progression	+ (HSE)	[46, 47]
	DD IRIS/relapse cryptococcal meningitis	+	[51]
Multiple sclerosis	Diagnosis	–	[54–59]
	DD for neurological illness with similar symptoms	+	[59]
	Progression	–	[54–59]
	IL-6 polymorphisms	−/+	[60–62]
SLE/neuro-lupus	Diagnosis of neurological involvement	+	[64–73]
	Progression	+/–	[64, 69, 71, 72]
	IL-6 polymorphisms	+/–	[74]
Traumatic brain injury	Prognosis	+	[76–80]
	IL-6 polymorphisms/prognosis	−/+	[81, 82]
Ischemic stroke	Diagnostics/extent	+	[83–89]
	Prognosis	+	[83, 87, 88]
	Relevance of IL-6 polymorphisms	–	[90–94]

CSF-IL6, Cerebrospinal fluid IL-6; CNS, central nervous system; HSE, herpes simplex encephalitis; DD, differential diagnosis; IRIS, immune reconstitution inflammatory syndrome; SLE, systemic lupus erythematosus.

response subsiding [80]. Smaller study sizes, inclusion of polytrauma versus isolated TBI, presence of a subdural hematoma, the age of the patient [80] or the type of CSF collection (continuous versus intermittent) [95] could also be factors responsible for the different results.

At this point, the relevance of IL-6 polymorphisms for the prognosis of TBI patients is a controversial issue. Studies focused primarily on the 174C/G and 596G/A polymorphisms. Given the current, contradictory results, further studies would be required to confirm unambiguous associations.

The initial CSF IL-6 increase in patients with cerebral ischemia correlates with the size of the brain lesion as well as with the clinical outcome, and could thus be used as a prognostic marker. According to one study, the early increase allows for the prognostic assessment of the patient – even before any radiological changes are visible. Even though these findings imply a high potential clinical benefit, here, too, further studies will be necessary to evaluate the clinical application and establish cutoffs for assessment.

With respect to IL-6 polymorphisms, study results have been contradictory and two meta-analyses could find no association between IL-6 polymorphism and risk for ischemic stroke.

Table 1 shows a summary of the current assessment of CSF IL-6 for the application areas described.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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