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Research Article

Targeting the IL-6/STAT3 Signaling Pathway by Anti-IL-6 Receptor Antibody (Tocilizumab) in the Treatment of Multiloculated Hydrocephalus

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Abstract

Background: Multiloculated hydrocephalus is characterized by progressive proliferation of multiple intraventricular septations, thus resulting in the multiple cystic cavities observed in the ventricles. Surgical management is performed neuroendoscopically by creating fenestrations between the cavities to decrease the number of shunts used. However, intraventricular septations continue to proliferate leading to the requirement of multiple revision surgeries that are associated with increased morbidity and mortality.

Purpose: To conduct a literature review prior to the initiation of the preclinical and clinical research for the underlying pathophysiological and biochemical changes associated with multiloculated hydrocephalus, aiming to target the disease by a pharmacological agent capable of inhibiting theses changes.

Methods: Literature search was done through PubMed. The following areas were searched: multiloculated hydrocephalus, diseases with similar causative factors as multiloculated hydrocephalus and known biochemical changes, and pharmacological agents targeting the pathogenesis of the diseases.

Results: Chronic inflammatory process in the form of ventriculitis in multiloculated hydrocephalus leads to subependymal glial cells proliferation and projection of these glial tissues into the ventricles forming multiple septations. In other inflammatory diseases and inflammatory cancers with elevated levels of IL-6, activation of IL-6/STAT3 signaling pathway resulted in cells proliferation and inhibition of apoptosis. The Food and Drug Administration (FDA) approved the use of Tocilizumab an IL-6 Receptor antibody (IL-6R antibody) in inflammatory autoimmune diseases. Also, clinical trials on the use of Tocilizumab in some CNS disorders are going on.

Conclusion: Progressive proliferation of intraventricular septations in multiloculated hydrocephalus is probably due to chronic inflammatory process and activation of IL-6/STAT3 signaling pathway. So, Tocilizumab an IL-6R antibody might suppresses the proliferation of intraventricular septation. Further studies are needed to test whether Tocilizumab will suppress the chronic ventriculitis in multiloculated hydrocephalus and glial cell proliferation.

Keywords: Post Infection Hydrocephalus; Multiloculated Hydrocephalus; Gliosis; IL-6/STAT3; IL-6R Antibody

Introduction

Multiloculated hydrocephalus is one of the most challenging diseases in neurosurgery. Until now there has been no definitive curative treatment due to the progressiveness of the disease. Hydrocephalus is defined as accumulation of CSF in the ventricles, which will lead to increased ventricular pressure, resulting in ventricular dilatation, it might then progress to compress surrounding neural tissues, leading to neurological deficits. Multiloculated

hydrocephalus is a type of hydrocephalus in which in addition to all features of hydrocephalus mentioned above, there are multiple separated cystic cavities or spaces, isolated by multiple intraventricular septations, located in or in relation to the ventricular system, and filled with CSF. Historically and till the present time the only definitive treatment for multiloculated hydrocephalus is surgical. The aim of surgical treatment is to drain the ventricular cavity by shunting, and to create fenestrations between adjacent compartments by neuroendoscopy, opening multiple compartments into a single cavity, thus decreasing the number of shunts [1,2,3,4]. However, despite all these treatments the septations continue to proliferate leading to accumulation of CSF in isolated compartments, compressing surrounding neural tissues. As a result, there is a need for revision surgery later on, which is associated with increased risk of morbidity and mortality. Regarding this, Spennato et al. proposed that the cause behind shunt obstruction in multiloculated hydrocephalus is the chronic inflammation at ependymal level that persists for a long time [3]. This chronic inflammation results in the formation of new septa thus leading to further obstruction [3]. Therefore, he considered multiloculated hydrocephalus to be a progressive disease [3]. In addition, until the present time there has been no role of medical therapy in the treatment of multiloculated hydrocephalus except for antibiotics used to treat meningitis or shunt related infections. There are multiple studies in literature highlighting the surgical treatment of the disease. However, no study targeted the pathogenesis of this progressive disease by medical therapy.

Objectives

This study was conducted to search the literature for the possibility of introducing a medical treatment in the form of anti-inflammatory, chemotherapy, immunotherapy, or biological agents targeting the underlying pathophysiology of the progressive nature of septa formation and suppressing the chronic inflammation that occurs. Furthermore, if one of these agents proved to have a promising use, further research will be conducted in vivo to test its efficacy. This form of treatment will either be used as adjuvant to prevent further septa formation or as a primary treatment to render its formation from the start or both. 'The hypothesis of this research is: there is a scientific role of medical treatment in the management of multiloculated hydrocephalus by inhibiting progressive septa formation'. The outcome is that there might be a role of medical therapy by IL-6R antibody (Tocilizumab) in the treatment of multiloculated hydrocephalus. It targets the IL-6/STAT3 pathway, which is responsible for the inflammatory process sequelae. This finding has a promising impact on the outcome and prognosis of this progressive disease, since it will target the initiating pathophysiology. In addition, it will open the door for a new era of treatment for neurological and neurosurgical diseases.

Methodology

Literature search was done through PubMed. First, data about multiloculated hydrocephalus were collected including: definition, etiology, pathophysiology, management and prognosis. Due to the lack of available data on the biochemical changes associated with multiloculated hydrocephalus, search was done for diseases with similar causative agents and known molecular pathogenesis. Lastly, another search was undertaken to find whether there is any medical treatment targeting the pathogenesis of the diseases.

Results

Etiology and pathogenesis of multiloculated hydrocephalus

The core underlying pathogenesis of multiloculated hydrocephalus is an 'inflammatory process', and the inflammatory stimulus might be either infectious or chemical. It is triggered by other disease insults to the central nervous system such as: meningitis (mostly bacterial meningitis), intraventricular hemorrhage, shunt-related infections, overdrainage, direct ependymal trauma during catheter insertion and intracranial surgery [3,6]. The first two account for most of the cases. This inflammatory reaction will then lead to ventriculitis, which reactivates fetal mechanisms of germinal matrix glial cell proliferation and migration. Furthermore, inflammation of the ependyma stimulates proliferation of subependymal glial tissues [1]. In addition, destruction of ependymal cells triggers the onset of septa formation by allowing the proliferating glial tissues to project into the ventricles. This forms a nidus for the formation of septations that span the ventricles and obstruct vital foramina and CSF passages [2,6]. Moreover, intraventricular septations are also formed by the accumulation of inflammatory exudates and debris on the glial projections forming isolated compartments in the ventricular system. It takes ventricular septations an average of 2-4 months to form following ventriculitis [6]. As a result, anatomy of the ventricular system will change. Also, the normal flow of cerebrospinal fluid will be altered leading to the accumulation of cerebrospinal fluid within a loculated cavity; resulting in obstructive hydrocephalus, with progressive dilatation and mass effect on the adjacent parts of the brain.

Pathology of multiloculated hydrocephalus

Microscopically the septations are membranes composed of fibroglial tissues and round and polymorphonuclear cells [6]. In addition, features of chronic ventriculitis usually present in the form of subependymal gliosis and glial tufts extending through the destructed ependyma into the ventricular lumen [6].

Reactive gliosis and multicellular response to CNS damage and disease

Reactive gliosis refers to responses of glial cells associated

with CNS injury or disease. When CNS insult occurs, there are multicellular responses divided into three overlapping phases: 1) cell death and inflammation, 2) cell proliferation for tissue replacement, and 3) tissue remodeling [8]. The second and third phases are important because the proliferation of fibroblast-lineage cells, various type of glia including scar-forming astrocytes, and scar organization occur in these phases. Formation of compact astrocyte scar (glial scar) is a specialized aspect of reactive astrogliosis that occurs in response to severe tissue damage and leukocyte infiltration and involves phases of cell proliferation and cell organization [8]. There are multiple molecules that trigger astrocyte proliferation and astrocyte scar formation one of them are the IL-6 released by local cells and leukocytes [8]. In addition, organization of newly proliferated astrocytes into compact scars is by signals of IL-6 receptor-STAT3 signaling system [8].

IL-6 cytokine and IL-6/STAT3 pathway

Interleukin-6 (IL-6) is a multifunctional cytokine protein [9]. It has a role in inflammation and infection responses, regulation of immune system, neural processes and promotion of tumorigenesis [9,13,14,15]. Also, IL-6 was found to be elevated in a number of diseases: infections, autoimmune diseases, some solid cancers, neurological diseases, and tissue aging [11,14,15,16]. IL-6 receptors (IL-6R) is a protein with a ligand-binding IL-6 receptor chain, and a signal-transducing subunit gp130 [9]. However, binding of IL-6 to the IL-6R does not activate the signaling cascade. It is the binding of the IL-6 with IL-6R associated protein gp130 forming a complex that activates the intracellular signaling via JAK/STAT pathway [14]. Furthermore, it was found that activation of the STAT pathway is the one that leads to the anti-inflammatory effect of IL-6 in the form of: 1) activation of cell proliferation, and 2) inhibition of cell apoptosis [13,14]. Thus, it leads to tissue regeneration.

Anti-interleukin-6 receptor antibody (Tocilizumab)

Tocilizumab is a humanized monoclonal antibody [16]. It can block all signaling pathways of IL-6 by inhibiting the binding of IL-6 to IL-6R [16]. It has been proven clinically that Tocilizumab can be effective in the treatment of various diseases and can significantly reduce the inflammation associated with rheumatoid arthritis [23,24,25] and systemic juvenile arthritis [26,27]. Also, studies have been done to test the use of Tocilizumab in the treatment of some malignancies showing increased levels of IL-6 with activation of the STAT3 signaling pathway in order to inhibit the tumorigenesis and to suppress aggressive inflammatory cancers [19,20,21]. Safety profile of Tocilizumab was studied on patients with rheumatoid arthritis treated with this agent [28]. The most common side effects are: upper respiratory tract infection, nasopharyngitis, headache and hypertension [17]. The severe life threatening side effects are: serious infections, gastrointestinal perforations and hypersensitivity reactions including anaphylaxis [17]. On the other hand, there has not been an associated increase in the incidence of malignancy, tuberculosis activation or hepatitis.

IL-6 in CNS diseases

IL-6 was found to be elevated in a number of CNS conditions: infection, inflammation and malignancy. A study done to identify the relationship between the cytokines in the plasma and CSF, showed that ventriculostomy-related infection was associated with CSF IL-6 > 10,000 pg/ml (P value highly significant) [10]. This study concluded that infections have an important influence on cytokine production specially IL-6 and measurements of CSF IL-6 can be used as a marker for ventriculostomy-related infections [10]. Furthermore, a study was conducted on patients with sporadic amyotrophic lateral sclerosis, which is an inflammation of the CNS with infiltration of inflammatory cells in the spinal cord [12]. Tocilizumab infusion was given to the subject. Results supported research hypothesis that Tocilizumab infusions may benefit these patients by normalizing IL-6 expression [12]. Finally, ependymoma is a childhood brain tumor with poor prognosis. Ependymoma group A is an aggressive type and studying its molecular level revealed an inflammatory response [11]. Also, IL-6 and STAT3 pathway genes enriched the ependymoma group A, indicating an activation of the IL-6/STAT3 mechanism in this group which is responsible for the inflammation [11]. In addition, ependymoma cell growth was shown to be dependent on the IL6/STAT3 pathway as pharmacological inhibition of STAT3 resulted in blockage of the proliferation and induction of apoptosis [11].

Discussion

Data retained from the literature search indicate that there is ground for the utilization of Tocilizumab in the treatment of multiloculated hydrocephalus. Since there are no studies about the cellular and molecular basis of multiloculated hydrocephalus, but there is evidence that underlying cause of progressive intraventricular septations is ventriculitis [6], we search the literature for diseases caused by similar underlying pathophysiology with known biochemical changes. Results showed that ventriculostomy-related infection was associated with CSF IL-6 > 10,000 pg/ml which is significant [10]. Also, IL-6 activation of the STAT3 in response to CNS insult is the signaling pathway that triggers astrocyte proliferation and astrocyte scar formation [8]. Correlating these data we hypothesize that the etiological factor of multiloculated hydrocephalus initiates an inflammatory response that persists and elevates CSF IL-6 level, activating IL-6/STAT3 signaling pathway. Furthermore, the inflammation is chronic and ependymal cells lining the ventricle are exposed to elevated levels

of cytokines specifically IL-6 which might be the cause of progressive formation of intraventricular septations through IL-6/STAT3 which promotes cell proliferation 'astrocytes', inhibits apoptosis, and organized compact astrocyte scar. All these mechanisms may be the cause of progressive intraventricular septa formation. Furthermore, Tocilizumab is a humanized monoclonal antibody [16], that block all signaling pathways by inhibiting the binding of IL-6 to IL-6R [16] and has been approved by the FDA for the treatment of some inflammatory diseases associated with increased levels of IL-6 and other cytokines like rheumatoid arthritis and systemic juvenile arthritis. This agent decreased the inflammation associated with these diseases, maintained disease remission and slowed the progression of disease manifestation. Moreover, trial studies have been carried out on using Tocilizumab in CNS diseases associated with inflammation and elevated levels of IL-6 like in sporadic amyotrophic lateral sclerosis and ependymoma.

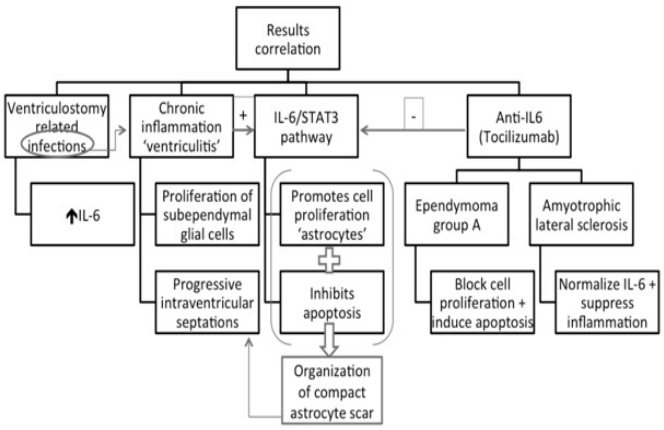

Figure 1: Diagram linking result findings.

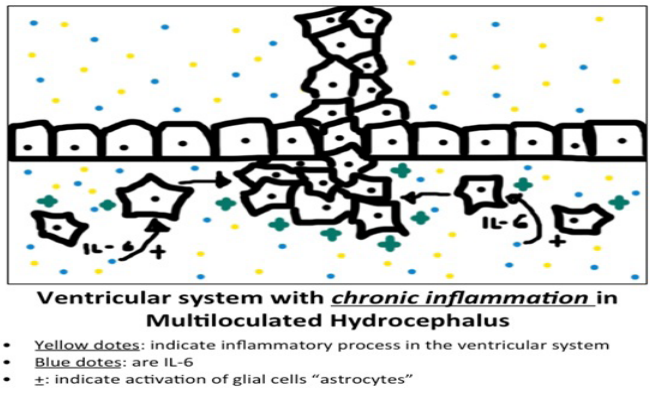

Figure 2: Schematic diagram showing inflammatory process effects in Multiloculated Hydrocephalus.

These studies showed that Tocilizumab normalized the IL-6 level and suppressed the inflammation. Also, in ependymoma inhibition of the IL-6/STAT3 pathway blocked cell proliferation and induced apoptosis. From these data we hypothesize that since multiloculated hydrocephalus is a chronic inflammatory disease with progressive growth of intraventricular septations due to gliosis possibly as in other CNS insult by activation of IL-6/STAT3 signaling pathway, Tocilizumab can stop progressive growth of intraventricular septations by blocking IL-6/STAT3 signaling pathway which is responsible for the astrocyte 'glial' scar formation. As a consequence, an improvement in the prognosis of this debilitating disease can be achieved while minimizing the need for repeated surgical intervention that is associated with high morbidity and mortality.

Conclusion

Progressive proliferation of intraventricular septations in multiloculated hydrocephalus is probably due to a chronic inflammatory process and activation of IL-6/STAT3 signaling pathway. Hence, Tocilizumab (an IL-6R antibody) might suppress the proliferation of intraventricular septations and decrease the neurological deficits associated with cystic compression on adjacent neural tissue. Also, decreasing the need for surgery and multiple shunt insertion that is associated with increased risk of infection, failure and increased morbidity and mortality.

Further clinical studies are essential to prove or reject the hypothesis of this research. First, a study should be conducted to measure the level of IL-6 in the CSF of patients with multiloculated hydrocephalus after resolution of meningitis or any other form of infection in order to find out if IL-6 has a role in chronic ventriculitis leading to septa formation in multiloculated hydrocephalus. Second, if it is proven that CSF IL-6 levels are high in these samples, treatment of half the sample with Tocilizumab and the other half with placebo is essential in testing the efficacy of Tocilizumab in inhibiting the growth of intraventricular septations. Finally, a clinical trial performed on humans would then be required to prove the safety and efficacy of Tocilizumab as a novel drug in the treatment of multiloculated hydrocephalus.

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