



The History of Cerebrospinal Fluid Analysis in Multiple Sclerosis: A Great Development over the Last Centuries

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Abstract

Cerebrospinal Fluid (CSF) analysis acquired a great role in the 1990's when applied to Multiple Sclerosis (MS) diagnostic work-up. The "watery fluid" by Andreas Vesalius remained unstudied till the introduction of Lumbar Puncture (LP) at the eighteenth century. Technical developments exploded in the 1990's: When new applications to the CSF analysis opened to the hypothesis of MS as the model of intrathecal synthesis of immunoglobulins. Over the last decades liquor findings remained of interest in MS not only for supporting diagnosis but also for their possible role as markers for disease prognosis.

Keywords

Lumbar puncture, History of neurology, Multiple sclerosis

Text

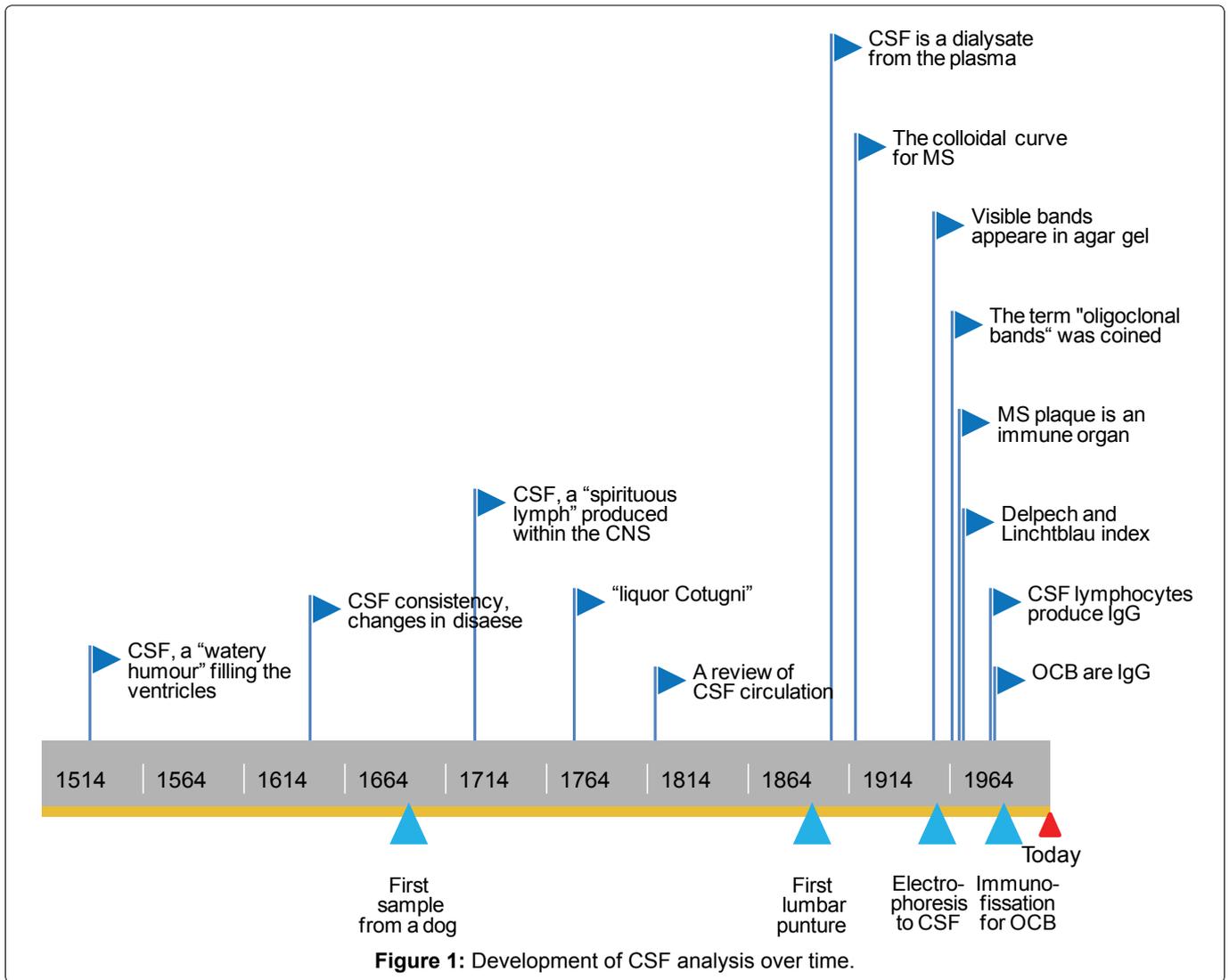
The existence of the Cerebrospinal Fluid (CSF) dated back to Hippocrates (460-375 before Christ, Greece), in relation to the drainage in hydrocephalus. Despite this early report, brain anatomy was described during the sixteenth and seventeenth centuries, including the first descriptions of a "watery humour" and "spirituous lymph" filling the ventricles written by Andreas Vesalius (1514-1564, Belgium), and Emanuel Swedenborg (1688-1772, Sweden) [1]. The lumbar puncture was introduced contemporarily by Walter Wynter (1860-1945, UK) and Heinrich Quincke (1842-1922, Germany), but this techniques remained applied for one century only to the diagnosis of meningitides, and the treatment of hydrocephalus [2,3]. Then, in 1912, William Mestrezat (1883-1928, France) described CSF chemical composition as a dialysate in osmotic equilibrium with plasma [4]. The innovation came with Karl Friedrich Lange (1883-1953, Germany), who studied qualitatively CSF proteins with "colloidal gold" test according to flocculation. The resulting curves were affected by presence of CSF gamma globulin, but not by albumin, alpha or beta globulins, and had a specific shape appearances in neurosyphilis and MS, that were called "dementia paralytica formula" [5]. Thirty years later, Elvin Kabat (1914-2000, USA) applied the electrophoretic techniques to CSF confirming the presence of increased gamma globulins in neurosyphilis and MS, thus opening to the hypothesis of the production of Immunoglobulins (Ig) within the CNS [6]. Furthermore, he estab-

lished the normal ranges for CSF albumin and Ig [7,8]. Electrophoresis had a great development in the middle of the nineteen century with the agar technique by Denise Karcher. In 1960 her co-worker Armand Lowenthal (1919-2001, The Netherland) applied electrophoresis to CFS assessing qualitatively abnormal proteins in MS. Increased gamma globulins were divided into fractions with different mobility in agar gel that appeared as visible bands [9,10]. The term Oligoclonal Bands (OCB) was coined by Christian Laterre (1933-1998, Belgium) [11,12]. In 1972, the focusing technique substituted agar gel: Proteins separated according to their isoelectric point and OCB were detected with higher sensitivity [13]. While Lowenthal was working at electrophoresis, Wallace Tourtellotte (1933, USA) focused on the MS demyelinating plaque in the Central Nervous System (CNS) as an immune organ, able to synthesize oligoclonal Ig type G (IgG) detectable in CSF and not in serum. In 1970 Tourtellotte proposed a formula to measure permeability across the Blood-Brain Barrier (BBB) using the albumin ratio [14,15].

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Few years later, investigators tried to determine the range of intrathecal synthesis comparing concentrations of IgG and albumin in CSF and serum. Historically this ratio, or IgG index, was called "Delpech and Lichtblau" index [16]. Despite this index was elevated in the 70% of MS patients, OCB were selected as the most reliable marker for MS by Hans Link (Sweden) in 1987. He also identified OCB in the gamma region as IgG, and recommended to compare bands patterns in CSF and serum to evidence intrathecal synthesis [17]. Moreover, Link recently confirmed the high sensitivity and specificity of OCB determined by isoelectric focusing for MS, detectable in more than 95% of the patients [18]. Support to this finding was given by Magnhild Sandberg-Wollheim (1937, Sweden) who studied *in vitro* MS CSF lymphocytes, discovering they produced increased IgG that migrated in the gamma region too (as *in vivo* IgG) with isoelectric focusing [19,20]. CSF analysis detecting intrathecal synthesis became then the gold standard test in suspected MS. A time-line of the historical development of CSF analysis is presented in Figure 1. Nowa-

days liquor findings are not straightly recommended to diagnose MS (except for the progressive forms), and CSF gained a role in the search for biomarkers related to disease prognosis. The idea of predicting disability and neurodegeneration, instead of defining the among of inflammation the early phases, pointed out again the role of liquor analysis. For example, neurofilaments' levels, especially of the light subunit, resulted elevated in the progressive forms: This finding suggested a biomarker that could reflect the axonal damage since the time of MS diagnostic work-up [21]. The need of monitoring and predicting MS prognosis allowed CSF to remain a key part of the MS history over time.

In conclusion, the interest in CSF increased rapidly both in clinical practice and in research when LP was introduced to collect samples in humans. Analytical techniques developed rapidly in the twentieth century, and have been immediately applied to CSF analysis. MS diagnostic work-up has been significantly enriched with liquor indexes and OCB detection. Moreover the extensive research around CSF anticipated, generated, and

strengthened the crucial hypothesis of MS as an autoimmune disease mediated by clonally expanded lymphocytes.

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