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Mechanism of subdural effusion evolves into chronic subdural hematoma: IL-8 inducing neutrophil oxidative burst

Zhiqiang Tao [a,*], Yingying Lin [b], Maotong Hu [a], Shenghong Ding [a], Jianwei Li [a], Yongming Qiu [b]

[a] Department of Neurosurgery, Yiwu Central Hospital, Wenzhou Medical College, Yiwu 32200, Zhejiang Province, People's Republic of China
[b] Department of Neurosurgery, Renji Hospital, School of Medicine, Shanghai Jiao-Tong University, No. 1630, Dongfang Road, Pudong New District, Shanghai 200127, People's Republic of China

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ABSTRACT

Chronic subdural hematoma (CSDH) is still a mysterious disease. Though great success has been has achieved by neuro-surgery treatment, the origin and development of CSDH remains unknown. Tremendous clinical observations have found the correlation of subdural effusion (SDE) and CSDH. However, systematic elucidation of CSDH's origin and progression is lacking while almost all the current hypothesis only explained partial phenomenon. This hypothesis proposes Interleukin (IL)-8 inducing neutrophil respiratory burst is the crucial impact when SDE evolves into CSDH. IL-8 initially secreted by dural border layer cells, accumulates and the concentration of IL-8 rises in the SDE cavity. Accompanied by the formation of neo-membrane under the dura meninges, IL-8 firstly prompts to establish the neo-vasculature in it, and then attracts lymphocytes aggregation in the neo-membrane. Both the newly recruited lymphocytes and endothelial cells assist the further elevation of local IL-8 concentration. When the IL-8 concentration elevated to a particular level, it attracts neutrophils to the inner wall of neo-vessels and primes them to oxidative burst. Lysosomes and superoxide released by these neutrophils make the fragile neo-capillary became leaky, and subsequently the plasma and blood cells run into SDE. However, as long as the erythrocytes come into the cavity, they shall bind large quantity of IL-8 and decrease IL-8 concentration to a lower level relatively that reduce the neutrophils recruit. When this negative feedback is stagnancy, for example, the SDE space is so large in elder man who is experiencing brain atrophy, the neo-vessels have to release more erythrocytes to bind IL-8, the liquid cavity will expand and the high intracranial pressure symptoms appeared. Our hypothesis holds potential for the proper therapeutic intervention of CSDH. IL-8 antagonist and other anti-inflammation drugs like macrolides antibiotics, glucocorticoid and atorvastatin might be optional to resist the liquid cavity expanding as actually occurs obvious bleeding soon.

Introduction

Chronic subdural hematoma (CSDH) is a common disease that often preceded by mild head injury, characterized by blood in the subdural space that accompanied with local inflammatory reaction [1,2]. The origin of CSDH is generally a subdural effusion (SDE). Nowadays, more and more evidences suggest that SDE and CSDH as two stages of the same inflammatory reaction and CSDH develops from inflammatory bleeding of microcapillary of SDE outer-membrane [3–5]. Although neoformation of subdural membrane, abnormal vascular permeability, hyperfunction of fibrinolysis and increasing content in the hydroma are traditionally cited explanations of pathogenesis of CSDH [3], the critical factors impacting the process of SDE evolves into CSDH remains unknown.

SDE encapsulates collections of effusion with neo-membrane and locates between the dura matter and arachnoid [6]. The out membrane of SDE contains multiple components, especially fragile neovasculature and fibroblasts which may influence the formation of a hematoma [7–8]. CSDH is also characterized by a high concentration of vascular endothelial growth factor (VEGF) in the fluid collection, possibly related to extensive angiogenesis in the hematoma membranes [9]. But it remains unsolved that why CSDH still self-resolved when concentration of VEGF is high. Moreover, Golden et al. found increased Interleukin (IL)-6 and IL-8 concentrations in CSDH fluid and attributed CSDH pathogenesis to an inflammatory reaction of the dural border layer cells [8]. Frati et al. also

* Corresponding author at: No. 699, Middle Jiangdong Road, Yiwu City, Zhejiang Province, People's Republic of China. Tel.:+86 0579 85209806; fax: +86 0579 85209610.
E-mail address: 266181@163.com (Z. Tao).

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identify a correlation between inflammation and CSDH recurrence [10].

Despite intensive research and subsequent advances in the surgical techniques of CSDH, its outcomes may not be very satisfactory because of recurrence and physical infirmity associated with aging [11]. Meanwhile, nonsurgical treatments, such as steroids, are attracting extensive attention, as they have the potential to reduce post-operative recurrence or even replace the need for surgery in selected patients [12]. Therefore, our hypothesis illustrates CSDH pathogenesis from the inflammatory point of view and might offer a new therapeutic strategy.

Hypothesis

This hypothesis proposes CSDH evolved from SDE is caused by IL-8 induced priming of neutrophil respiratory burst (Fig. 1). Local elevation of IL-8 concentration was found in the subdural space of both SDE and CSDH and the levels in CSDH was much higher (about 10 times) than in SDE, suggesting that IL-8 may be involved in the continuous development from SDE to CSDH and propagation of CSDH [13]. Meanwhile, IL-8 has a dose-dependent function of attracting of lymphocytes and neutrophils [14]. T lymphocytes were two to ten times more sensitive to IL-8 than neutrophils [14]. IL-8 has also been reported to induce neo-vascularization [15]. Therefore, we propose that IL-8 initially secreted by dural border layer cells (Fig. 2A), accumulates and prompts growth of neo-vessels along the outer membrane (Fig. 2B). Then, local elevation of IL-8 concentration recruits lymphocytes and endothelial cells to the neo-membrane (Fig. 2C). In clinical study, we observed many neutrophils adhering to the inner walls of the neo-vessels, but they rarely found outside the neo-vessels (Fig. 2D). We further proposed that oxidative burst might be happen in these neutrophils inside the walls of neo-vessels. Lysosomes and superoxide released by the neutrophils make the fragile neo-capillary became damaged and the plasma and blood cells run into the subdural space (Fig. 2E).

The erythrocytes have been found with extreme high affinity for IL-8 [16]. Therefore, as long as the erythrocytes come into the space, they shall bind large quantity of IL-8 and decrease free status IL-8 concentration to a lower level that fail to recruit neutrophils. Thus, there are lots of asymptomatic CSDH presence and be resolved spontaneously at sub-clinical condition. When this negative feedback is stagnancy, for example, the SDE space is so large in elder man who is experience brain atrophy, or the person who is taking anti-platelet or anti-coagulation medicine, the neo-membrane has to release more erythrocytes to bind IL-8 or failed to stop bleeding. Then we can see the liquid cavity will expand and the patients appear high intracranial pressure symptoms.

Our hypothesis provides potential for the proper therapeutic intervention of CSDH. IL-8 antagonist and other anti-inflammation drugs like macrolides antibiotics, glucocorticoid and atorvastatin might be optional to prevent SDE out-membrane neo-vessels bleeding speedily. And a relative slow bleeding process may avoid symptomatic CSDH taking place.

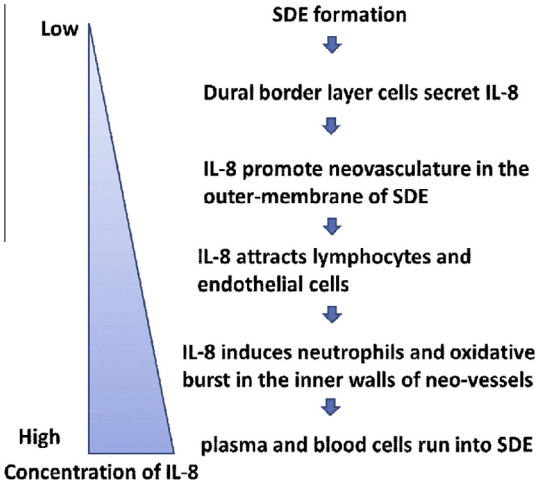

Fig. 1. Schematic figure of SDE evolved into CSDH.

Implication of hypothesis

Despite CSDH evolved from SDE is gradually accepted by researchers [17–19], the mechanism of inflammatory bleeding of outer-membrane of SDE remains unknown.

The inflammation response is a defense mechanism that protects them from infection or injury [20]. Ruptured arachnoid membrane with permitting cerebrospinal fluid effusion is the major injured tissue during SDE [21]. However, arachnoid membrane is a delicate structure with non itself-vascular tissue which implies that it has to take advantage of surrounding nutrients to repair [22]. However, the repair cannot be done when nutrients is not sufficient. The inflammatory bleeding of neo-capillary of SDE outer-membrane is reasonable explanation of providing sufficient nutrients for arachnoid membrane repair. Blood contains a variety of nutrients, such as proteins, vitamins, hormones, oxygen, and oxygenated hemoglobin [23]. We postulate this might be the cause of inflammatory bleeding.

The dural border layer cells locating on the dura-arachnoid interface secretes IL-8 and IL-6 and make the concentration elevated in SDE [24]. IL-6 promotes the proliferation of dural border layer cells and thickens of neo-membrane. IL-8 mainly stimulates neo-vasculature and recruits lymphocytes into neo-membrane which change the local inflammatory factors. When the concentration of IL-8 is high enough, it attracts neutrophil to accumulate inside the neo-vasculature. Then IL-8 binds to neutrophils which located in the inner wall of neo-capillary and primes of the oxidative burst. Released lysosomal enzymes and superoxide after neutrophils breakdown make the permeability of neo-vasculature greatly elevated. Subsequently the blood cells and plasma released into SDE, making it become hematoma.

The erythrocytes have large quantity of IL-8 receptors [16]. As long as erythrocytes enter the SDE, it will absorb free state IL-8 in SDE and hinder subsequent neutrophil attraction. This is a rapid negative-feedback.

Although CSDH has this effective rapid negative feedback. We are more concerned about the issues when or what goes wrong that causing symptomatic CSDH. We postulate that SDE cavity might be too large and make the rapid negative feedback stagnant. This is probably the major reason which causes CSDH clinical symptoms. When SDE cavity is large enough, the negative feedback delayed, the mount of bleeding increase and finally developed chronic high intracranial pressure symptoms.

In accordance to a lots of cases of SDE developing to CSDH, we proposed that the process of SDE evolving into CSDH can be divided into five stages (Fig. 3): (I) SDE formation stage: SDE happen and rise in size till its maximum state. Stage I persists about two weeks. (II) SDE steady stage: a period of time after SDE volume reaches its maximum. CT scan reveals similar density of SDE and CSF. The size of SDE in this stage is relatively stable. (III) SDE density elevating slowly stage: the entire or local density of SDE under CT scan increased with or without reduced volume. The time that stage II and III lasts varied among SDEs. (IV) Dominant bleeding