Biofluid Biomarkers in Chronic Subdural Hematoma

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Chronic subdural hematoma (cSDH) is a common neurosurgical entity that typically affects elderly patients. Studies have sought to establish the factors associated with an increased risk of cSDH recurrence and/or which can aid in the prediction of neurological/functional outcomes.

chronic subdural hematoma prognosis recurrence biomarker

1. Introduction

Chronic subdural hematoma (cSDH) is a common neurosurgical entity that typically affects elderly patients and is increasing in incidence. The presenting symptoms of cSDH are variable but commonly include gait disturbances and mental deterioration as well as limb weakness [1]. The diagnosis of cSDH is based on imaging indicating the presence of a hematoma in the subdural space, often in association with a history of mild or moderate head injury, weeks to months prior to hospitalization [2]. Histologically, cSDH is characterized by an external and an internal membrane, encapsulating the hematoma, both containing fibroblast layers with only the former showing the persistent presence of immature, leaky vessels that have been postulated to drive hematoma expansion [3].

Surgical evacuation remains the standard of care for cSDH with immediate results postoperatively [2]. Nevertheless, the postoperative recurrence of cSDH is not uncommon, ranging between 5 and over 30% in previous studies [2]. cSDH recurrence thus currently represents a significant nosological consideration, the more so since reoperations increase healthcare-associated costs and are a substantial burden on patient morbidity and mortality [1][4]. In this context, previous studies have sought to establish the factors associated with an increased risk of cSDH recurrence and/or which can aid in the prediction of neurological/functional outcomes. Thus far, several clinical factors, e.g., increased patient age, radiological characteristics, e.g., bilateral hematoma, and specific external membrane features, e.g., enhanced presence of angiogenic factors, have been previously indicated as risk factors for cSDH recurrence [5][6][7][8]. Additional research has focused on identifying prognostic molecular or cellular factors within the hematoma fluid and/or peripheral blood of cSDH patients. This class of potential prognostic biofluid biomarkers includes molecules and/or cellular populations that are implicated in cSDH pathogenetic and pathophysiological processes such as cerebrospinal fluid leaks, inflammation and fibrinolysis [3][9][10]. While at present no such biomarker has been validated for clinical use, the overarching goal of this research field is to provide valuable tools guiding future clinical decision making in cSDH [11].

2. Biomarker Study Characteristics/Designs and Time Trends

Twenty-three studies published between 2003 and 2023 on a total of 3749 patients were identified in the present discussion. The median postoperative recurrence rate of 17.5% falls well within the range of previous estimates (5 to 30%) [2]. The notable limitations of the incorporated studies were their retrospective cohort/single-center designs (*n* =11 studies) and/or small cohort sizes (<100 patients, *n* = 12 studies).

A noteworthy trend is a shift in research focus towards circulating biomarkers on larger patient cohorts during the last four years (2020–2023: circulation focus in 12 of 13 studies, median patient size: 256 patients) compared with previous studies (2003–2018: circulation focus in 3 of 10 studies, median patient size: 63). While hematoma biomarkers allow for the analysis of local pathophysiological processes [3], the distinct advantages of assessing circulating prognostic biomarkers are the ease of sampling and that they offer the opportunity of tailoring patient treatment according to risk stratification preoperatively. In this context, current guidelines on cSDH treatment incorporate adjuvant drug therapies such as cholesterol-lowering statins and anti-inflammatory corticosteroids that are designed to improve patient neurological function and/or reduce recurrence [2][12]. From an analytical perspective, the protein analysis of biomarkers with significant findings ranged from single enzyme-linked immunosorbent [6][13][14], nephelometric [9] and electrochemiluminescent [15] assays to multiplex immunoassays [10][11][16].

3. Biomarkers in Recurrence Prediction

Numerous studies on biomarkers associated with inflammatory processes were identified. Enhanced levels of cytokine biomarkers in hematoma fluid have been highlighted as evidence for a robustly elevated local inflammatory index, as well as for the involvement of inflammatory processes in recurrence. The replication of findings was evident for IL-6 [6][13], with less consistent findings regarding the direction of change (increased or decreased levels) in recurrent cSDH for IL-8 and RANTES [10][11][13]. The notion of increased local anti-inflammatory activity (reflected by the levels of a panel of cytokine biomarkers) in association with reduced cSDH recurrence rates was introduced by the studies of a single group [10][16].

More recent studies assessing circulating cellular population ratios as markers of inflammation support the notion of a systemic inflammatory response in cSDH and its association with recurrence [17][18]. Thus, while Guresir et al. [17] proposed preoperative RPR as a novel independent predictor of cSDH recurrence, De Oliveira et al. [18] highlighted similar value for the postoperative NLR ratio. Of note, evidence for a systemic inflammatory response triggered by cSDH was previously obtained by studies comparing levels of cell inflammatory markers in patients and healthy controls [19][20].

Aside from the aforementioned cellular biomarkers, circulating eosinophil counts were indicated as independent predictors of recurrence by two studies, albeit with contradictory findings. Thus, Chen et al. [21] indicated that lower peripheral eosinophil counts are independently associated with recurrence, while Matsubara et al. [22] reported the

opposite. The findings of Chen et al. appear consistent with evidence suggesting a protective role of hematoma-membrane-infiltrating eosinophils against recurrence in a previous histological study [23].

A substantial body of evidence supports a role for local coagulation and fibrinolysis in cSDH development [24][25][26][27][28], including evidence for excessive activation of the former during the early stages of development, succeeded by hyperfibrinolysis [29]. In relation to cSDH recurrence, Katano et al. [14] found higher levels of TPA, a major fibrinolytic mediator, in the hematoma fluid of patients that experienced recurrences, while Wang et al. [30] indicated lower levels of circulating fibrinogen in their recurrent cases. Circulating FDP (but not D-dimer) levels on patient admission as an independent predictor for recurrence was indicated by Hori et al. [31]. The authors of this study hypothesized that the systemic elevation of FDP induces a systemic inflammatory response, which in turn influences expansion of the hematoma and can lead to its recurrence [31]. The potential of coagulation cascade mediators as peripheral biomarkers in the prediction of cSDH recurrence is further supported by studies reporting preoperative thrombocytopenia or increased PT as independent risk factors for cSDH recurrence [22][32][33] and of lower circulating factor XIII in recurrent cases [34].

The formation of immature, leaky vessels in the outer membrane of cSDH upon which damaging forces of inflammation and of abnormal cerebral pulsations are exerted has been postulated as a driving mechanism for cSDH expansion, as well as a risk factor for its recurrence [3][35]. A study indicating significantly lower postoperative levels of peripheral EPCs in patients that experienced cSDH recurrences suggested that this decrease may lead to a reduced capacity for endothelium repair, thus increasing the risk of cSDH recurrence [35]. Following a similar logic, an attenuated protective role on vascular integrity and endothelial function due to decreased peripheral HDL levels was postulated by a second study indicating lower HDL levels as an independent predictor of recurrence [36].

Three additional studies indicated the potential value of peripheral biomarkers as independent predictors of recurrence. The dehydration status of cSDH patients on admission, estimated using the blood U/Cr ratio, was reported as an independent predictor of cSDH recurrence by Mainka et al., 2022 [37]. The authors proposed that the impact of dehydration is due to a reduction in brain volume and/or instigation of inflammatory processes that predispose patients to the occurrence/recurrence of cSDH [37]. Wang et al. investigated BUN levels in cSDH patients based on previous findings indicating the prognostic significance of BUN in neurological disorders such as ischemic stroke [30]. Their findings indicated that an elevated postoperative level of BUN is an independent risk factor for recurrence via mechanisms that remain to be established [30]. Blood type A was also highlighted as an independent risk factor for cSDH recurrence by Hirai et al. [38]. Nevertheless, it is worth pointing out that a second study on another Asian cohort, reporting significantly lower recurrence rates, did not find an association between ABO types and cSDH recurrence [33]. Larger prospective cohort studies that may include additional population samples are warranted to establish the impact of ABO blood types on cSDH recurrence.

4. Biomarkers in Neurological/Functional Outcome Prognosis

A smaller number of studies assessed biomarkers in relation to cSDH patient neurological/functional outcome. The pilot study of Puccio et al. indicated strong correlations between higher hematoma IL-5 levels and more favorable GOS-E scores [11]. Interestingly, higher hematoma IL-5 levels were associated with lower rates of cSDH recurrence in two other studies included herein [10][16]. Consistent with the notion of a significant association between a lower preoperative peripheral inflammatory index and a favorable functional outcome are the findings of Guresir et al. [17], indicating significantly higher Karnofsky scores 3 months postoperatively in the low compared to the high RPR patient group. Moreover, Idowu et al. [39] indicated significant associations between a low admission PLR, which represents another inflammatory marker, and poor outcome at 3 months using the GOS and LABDES. Notably, in the same study, inflammatory markers, such as c-reactive protein (CRP) and the NLR, did not display associations with the outcome [39].

Lastly, on the basis of previous evidence for significant associations between admission circulating BNP-1 levels and functional outcome in neurological disease, including traumatic brain injury and stroke, Chihi et al. [15] investigated circulating peptide levels in cSDH. Their findings indicated that preoperative BNP-1 is an independent predictor of functional outcome at 5–6 months postoperatively [15].

References

1. Kolias, A.G.; Chari, A.; Santarius, T.; Hutchinson, P.J. Chronic subdural haematoma: Modern management and emerging therapies. Nat. Rev. Neurol. 2014, 10, 570–578.
2. Tamura, R.; Sato, M.; Yoshida, K.; Toda, M. History and current progress of chronic subdural hematoma. J. Neurol. Sci. 2021, 429, 118066.
3. Edlmann, E.; Giorgi-Coll, S.; Whitfield, P.C.; Carpenter, K.L.H.; Hutchinson, P.J. Pathophysiology of chronic subdural haematoma: Inflammation, angiogenesis and implications for pharmacotherapy. J. Neuroinflamm. 2017, 14, 108.
4. Weigel, R.; Schmiedek, P.; Krauss, J.K. Outcome of contemporary surgery for chronic subdural haematoma: Evidence based review. J. Neurol. Neurosurg. Psychiatry 2003, 74, 937–943.
5. Gandhoke, G.S.; Kaif, M.; Choi, L.; Williamson, R.W.; Nakaji, P. Histopathological features of the outer membrane of chronic subdural hematoma and correlation with clinical and radiological features. J. Clin. Neurosci. 2013, 20, 1398–1401.
6. Hong, H.J.; Kim, Y.J.; Yi, H.J.; Ko, Y.; Oh, S.J.; Kim, J.M. Role of angiogenic growth factors and inflammatory cytokine on recurrence of chronic subdural hematoma. Surg. Neurol. 2009, 71, 161–165.
7. Mishra, R.; Deora, H.; Florez-Perdomo, W.A.; Moscote-Salazar, L.R.; Garcia-Ballestas, E.; Rahman, M.M.; Shrivastava, A.; Raj, S.; Chavda, V.; Montemurro, N.; et al. Clinical and

Radiological Characteristics for Recurrence of Chronic Subdural Hematoma: A Systematic Review and Meta-Analysis. Neurol. Int. 2022, 14, 683–695.

8. Miah, I.P.; Tank, Y.; Rosendaal, F.R.; Peul, W.C.; Dammers, R.; Lingsma, H.F.; den Hertog, H.M.; Jellema, K.; van der Gaag, N.A. Radiological prognostic factors of chronic subdural hematoma recurrence: A systematic review and meta-analysis. Neuroradiology 2021, 63, 27–40.
9. Kristof, R.A.; Grimm, J.M.; Stoffel-Wagner, B. Cerebrospinal fluid leakage into the subdural space: Possible influence on the pathogenesis and recurrence frequency of chronic subdural hematoma and subdural hygroma. J. Neurosurg. 2008, 108, 275–280.
10. Pripp, A.H.; Stanišić, M. Association between biomarkers and clinical characteristics in chronic subdural hematoma patients assessed with lasso regression. PLoS ONE 2017, 12, e0186838.
11. Puccio, D.J.; Deng, H.; Eagle, S.R.; Okonkwo, D.O.; Nwachuku, E.L. Pilot Biomarker Analysis and Decision Tree Algorithm Modeling of Patients with Chronic Subdural Hematomas. Neurotrauma Rep. 2023, 4, 184–196.
12. Zhang, J.; Fei, Z.; Feng, H.; Gao, G.; Hao, J.; Hou, L.; Hu, J.; Huang, Y.; Jiao, B.; Ji, H.; et al. Expert consensus on drug treatment of chronic subdural hematoma. Chinese Neurosurg. J. 2021, 7, 47.
13. Frati, A.; Salvati, M.; Mainiero, F.; Ippoliti, F.; Rocchi, G.; Raco, A.; Caroli, E.; Cantore, G.; Delfini, R. Inflammation markers and risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma: A prospective study. J. Neurosurg. 2004, 100, 24–32.
14. Katano, H.; Kamiya, K.; Mase, M.; Tanikawa, M.; Yamada, K. Tissue plasminogen activator in chronic subdural hematomas as a predictor of recurrence. J. Neurosurg. 2006, 104, 79–84.
15. Chihi, M.; Gembruch, O.; Darkwah Oppong, M.; Rauschenbach, L.; Rauscher, S.; Jabbarli, R.; Wrede, K.H.; Sure, U.; Maslehaty, H. Role of brain natriuretic peptide in the prediction of long-term surgical outcome of chronic subdural hematoma. J. Neurol. Sci. 2021, 420, 117240.
16. Pripp, A.H.; Stanišić, M. The correlation between pro- and anti-inflammatory cytokines in chronic subdural hematoma patients assessed with factor analysis. PLoS ONE 2014, 9, 970468.
17. Güresir, Á.; Coch, C.; Heine, A.; Mass, E.; Lampmann, T.; Vatter, H.; Velten, M.; Schmitz, M.T.; Güresir, E.; Wach, J. Red Blood Cell Distribution Width to Platelet Count Ratio Facilitates Preoperative Prediction of Recurrence in Surgically Treated Chronic Subdural Hematoma. Front. Neurol. 2022, 13, 884231.
18. de Oliveira, A.J.M.; Solla, D.J.F.; de Oliveira, K.F.; Amaral, B.S.; Andrade, A.F.; Kolias, A.G.; Paiva, W.S. Postoperative neutrophil-to-lymphocyte ratio variation is associated with chronic subdural hematoma recurrence. Neurol. Sci. 2022, 43, 427–434.

19. Zhang, Y.; Yang, Y.; Long, S.; Li, G. Assessment of peripheral blood cell inflammatory markers in patients with chronic subdural hematoma. Clin. Neurol. Neurosurg. 2020, 191, 105738.
20. Fan, Y.; Wu, D.; Zhang, X.; Jiang, W.; Nie, M.; Liu, X.; Xiang, T.; Liu, M.; Chen, Y.; Feng, D.; et al. The inflammatory cellular feature in the peripheral blood of chronic subdural hematoma patients. J. Clin. Lab. Anal. 2022, 36, e24706.
21. Chen, S.; Shao, L.; Ma, L. Peripheral blood eosinophil and classification of residual hematoma help predict the recurrence of chronic subdural hematoma after initial surgery. Front. Surg. 2022, 9, 970468.
22. Matsubara, M.; Yagi, K.; Minami, Y.; Kanda, E.; Sunada, Y.; Tao, Y.; Takai, H.; Shikata, E.; Hirai, S.; Matsubara, S.; et al. Preoperative elevated eosinophils in peripheral blood for prediction of postoperative recurrence of chronic subdural hematoma. J. Neurosurg. 2023, 1, 1–6.
23. Davidson, B.; Narvacan, K.; Munoz, D.G.; Rotondo, F.; Kovacs, K.; Zhang, S.; Cusimano, M.D. The Crucial Role of Eosinophils in the Life Cycle, Radiographical Architecture, and Risk of Recurrence of Chronic Subdural Hematomas. Neurotrauma Rep. 2021, 2, 76–83.
24. Yamashima, T.; Kubota, T.; Yamamoto, S. Eosinophil degranulation in the capsule of chronic subdural hematomas. J. Neurosurg. 1985, 62, 257–260.
25. Murakami, H.; Hirose, Y.; Sagoh, M.; Shimizu, K.; Kojima, M.; Gotoh, K.; Mine, Y.; Hayashi, T.; Kawase, T. Why do chronic subdural hematomas continue to grow slowly and not coagulate? Role of thrombomodulin in the mechanism. J. Neurosurg. 2002, 96, 877–884.
26. Fujisawa, H.; Ito, H.; Kashiwagi, S.; Nomura, S.; Toyosawa, M. Kallikrein-kinin system in chronic subdural haematomas: Its roles in vascular permeability and regulation of fibrinolysis and coagulation. J. Neurol. Neurosurg. Psychiatry 1995, 59, 388–394.
27. Y, K.; M, C.; T, T.; Y, S. Coagulation and fibrinolysis in chronic subdural hematoma. Neurosurgery 1989, 25, 25.
28. Ito, H.; Yamamoto, S.; Komai, T.; Mizukoshi, H. Role of local hyperfibrinolysis in the etiology of chronic subdural hematoma. J. Neurosurg. 1976, 45, 26–31.
29. Suzuki, M.; Kudo, A.; Kitakami, A.; Doi, M.; Kubo, N.; Kuroda, K.; Ogawa, A. Local hypercoagulative activity precedes hyperfibrinolytic activity in the subdural space during development of chronic subdural haematoma from subdural effusion. Acta Neurochir. 1998, 140, 261–266.
30. Wang, N.; Hu, J.; Oppong-Gyebi, A.; Zhu, X.; Li, Y.; Yang, J.; Ruan, L.; Zhuge, Q.; Ye, S. Elevated blood urea nitrogen is associated with recurrence of post-operative chronic subdural hematoma. BMC Neurol. 2020, 20, 411.

31. Hori, Y.S.; Ebisudani, Y.; Aoi, M.; Fukuhara, T. Elevated Serum Fibrinogen Degradation Products on Admission Is a Novel Predictive Factor for Recurrence of Chronic Subdural Hematoma. World Neurosurg. 2018, 118, e753–e757.
32. Martinez-Perez, R.; Tsimpas, A.; Rayo, N.; Cepeda, S.; Lagares, A. Role of the patient comorbidity in the recurrence of chronic subdural hematomas. Neurosurg. Rev. 2021, 44, 971–976.
33. Ou, Y.; Yu, X.; Wu, L.; Zhang, D.; Liu, W. Recurrence of Chronic Subdural Hematoma Is Independent of ABO Blood Type: A Retrospective Cohort Study. Front. Neurol. 2022, 13, 833958.
34. Bosche, B.; Molcanyi, M.; Noll, T.; Kochanek, M.; Kraus, B.; Rieger, B.; El Majdoub, F.; Dohmen, C.; Löhr, M.; Goldbrunner, R.; et al. Occurrence and recurrence of spontaneous chronic subdural haematoma is associated with a factor XIII deficiency. Clin. Neurol. Neurosurg. 2013, 115, 13–18.
35. Song, Y.; Wang, Z.; Liu, L.; Wang, D.; Zhang, J. The level of circulating endothelial progenitor cells may be associated with the occurrence and recurrence of chronic subdural hematoma. Clinics 2013, 68, 1084–1088.
36. Liu, W.C.; Lin, Q.Q.; Jin, J.; Wang, M.; You, W.D.; Gu, J.; Pan, J.W. An association of low high-density lipoprotein levels with recurrence of chronic subdural hematoma. Acta Neurochir. 2021, 163, 1061–1068.
37. Mainka, N.; Borger, V.; Hadjiathanasiou, A.; Hamed, M.; Potthoff, A.L.; Vatter, H.; Schuss, P.; Schneider, M. Dehydration Status at Admission Predicts Recurrence in Patients with Traumatic Chronic Subdural Hematoma. J. Clin. Med. 2022, 11, 1178.
38. Hirai, S.; Yagi, K.; Hara, K.; Kanda, E.; Matsubara, S.; Uno, M. Postoperative recurrence of chronic subdural hematoma is more frequent in patients with blood type A. J. Neurosurg. 2021, 135, 1203–1207.
39. Idowu, O.E.; Oyeleke, S.O.; Vitowanu, J.M. Impact of inflammatory cell ratio, biomarkers, activated partial thromboplastin time and prothrombin time on chronic subdural haematoma severity and outcome. Eur. J. Trauma Emerg. Surg. 2022, 48, 1085–1092.