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ORIGINAL ARTICLE

Prediction of calcification tendency in pediatric cystic adamantinomatous craniopharyngioma by using inflammatory markers, hormone markers, and radiological appearances

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Abstract

Purpose To compare the different levels of inflammatory markers, hormone markers, and radiological appearances between PCACP with and without calcification so as to explore the relationships between these markers and calcification.

Methods The inflammatory markers, hormone markers, and radiological appearances were compared not only between PCACP with and without calcification, but also among its different forms of calcification. The receiver operating characteristic (ROC) curve was performed to evaluate the diagnostic significance of all markers between these groups.

Results It was showed that the white blood cell (WBC) count, neutrophil count, monocyte count, prognostic nutritional index (PNI), prolactin (PRL), and T1WI signal of cysts were higher in PCACP with calcification than in PCACP without calcification. The neutrophil count was significantly higher in PCACP with eggshell calcification than in other groups. The PCACP with mixed calcification had the highest PRL level in all kinds of PCACP with calcification. Only the area under curve (AUC) values of neutrophil count and PRL level were greater than 0.8.

Conclusion It is found that inflammation and hormone are related to PCACP's calcification. High neutrophil count and PRL level may indicate possible calcification tendency in PCACP. Improved intracystic therapies based on these results may help to inhibit the formation of calcification in PCACP in future.

Keywords Craniopharyngioma · Cyst · Calcification

Introduction

Craniopharyngioma (CP) is an epithelial tumor that arises along the craniopharyngeal duct. It accounts for 5.6–15.0% of all pediatric brain tumors. Although CP is classified as a World Health Organization (WHO) grade I neoplasm, its aggressive behavior and tendency to adhere to critical parasellar structure are conducive to recurrence even after total tumor removal, and its recurrence always leads to unsatisfactory postoperative life qualities for patients [1–4].

CP is histopathologically composed of adamantinomatous craniopharyngioma (ACP) and squamous papillary craniopharyngioma (PCP). Approximately 90% of ACP includes a cystic component. Nowadays, multiple efforts have been directed towards assessing the effectiveness of intracystic therapies, such as bleomycin and interferon-α [5–10]. Oppositely, ACP's calcification always tightly adheres to adjacent critical neurovascular tissues, increasing the rates of difficulties and injuries in operation. However, pediatric cystic ACP (PCACP) is most but not all cases with calcification. There may be some relationships between cyst and calcification. If calcification tendency could be diagnosed in PCACP preoperatively with less or none invasive method, the intracystic therapeutic method could be used timely to reduce the formation of calcification. Even if the tumor recurs, the second time surgery will be benefit from less calcification adhesion.

Ming Chen, Zhang Zhang and Min Yang contributed equally to this work.

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Therefore, the aims of this study were to analyze different preoperative inflammatory markers, hormone markers, and radiological appearances between PCACP with and without calcification and to explore the relationships between these markers and calcification in PCACP. These results may provide theoretical basis for improved intracystic therapies to inhibit the formation of calcification in PCACP in future.

Methods

Patients and healthy controls

Medical records of patients diagnosed with PCACP at Xinhua Hospital between January 2005 and January 2017 were collected and retrospectively analyzed in this study. All patients enrolled in the final analysis met the following criteria: (1) the age of patients ranged from 1 to 14 years old. (2) PCACPs were first time operated and totally resected in Xinhua Hospital. The total resection was judged by intraoperative observation under surgical microscope and postoperative images. (3) The pathological types of CPs were histologically verified in surgical specimens according to WHO grade criteria. Both cystic change and calcification were verified by preoperative images, intraoperative observation, and postoperative pathological diagnosis. The enrolled pediatric ACPs must have cystic changes. (4) No preoperative chemotherapy, radiotherapy, and hormone therapy including glucocorticoids. (5) No hematological diseases, current infectious diseases, hyperpyrexia, diabetes mellitus, metabolic syndrome, serious heart disease, hypertension, severe renal or hepatic dysfunction, cancer autoimmune diseases, inflammatory diseases, and medication usage related to inflammatory conditions. (6) Complete data of preoperative routine blood test, serum albumin, and hormone level. (7) Informed consents were obtained from eligible patients, and this study was approved by the institutional ethics committee.

Clinical data collection

Patients' data including age and gender were retrieved from retrospective medical records. Preoperative venous blood samples were routinely taken for blood routine test, hepatic function test, and hormone level test within 1 week of surgery as a part of the standard preoperative workup. All of the obtained samples were stored at< 20 °C, and tests were performed by the staff at the department of clinical laboratory of Xinhua Hospital within 2 h. The white blood cell (WBC), neutrophil, lymphocyte, monocyte, and platelet counts were collected from blood routine test. All the clinical inflammatory data mentioned above were collected by standardized automated counters. The albumin levels were collected from hepatic function test, and the adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), growth hormone (GH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), free triiodothyronine (FT3), and free tetraiodothyronine (FT4) were collected from hormone level test. Moreover, preoperative NLR (quotient of neutrophil count to lymphocyte count), dNLR [quotient of neutrophil count to (WBC count–neutrophil count)], PLR (quotient of platelet count to lymphocyte count), MLR (quotient of monocyte count to lymphocyte count), and PNI (albumin (g/L) + 5 × total lymphocyte count) were calculated.

Imaging data acquisition and analysis

Magnetic resonance imaging (MRI) was obtained with a 3.0-T MR scanner (Discovery 750, GE Healthcare). All the neuroimagines were studied using double-blind review procedure by two experienced neuroradiologists. They first reviewed all the images, and then resolved their discrepancies in consensus. Quantitative measurements were made on a picture archiving and communication system (PACS).

The size, shape, quantity, and signal of cystic component were evaluated by MRI appearances. The size, shape, and quantity of calcification were evaluated by CT appearances. Besides that, the calcification cyst ratio (CCR) (maximum diameter of calcification/maximum diameter of cyst) and the classification base on tumor's growth pattern were also evaluated. The maximum diameter of cystic component was measured on all levels of MR images. The shape of cyst was defined as spherical, lobular, and irregular by sagittal and coronal MR images. The signal intensity of tumor cystic fluid on T1-weighted images was described as hyper-, iso-, or hypointense comparing with the signal of gray matter. The maximum diameter of calcification was measured on all levels of CT images. Shape of calcification was defined as point or slice, eggshell, and mixture (contains both point or slice and eggshell calcification at the same time). The CCR was measured and calculated by PACS. The classification of tumor was divided into three groups which were infrasellar/infradiaphragmatic (Id), suprasellar subarachnoid extraventricular (Sa), and suprasellar subpial ventricular (Sp) referred to previous literature [11].

Statistical analysis

Statistical analysis was carried out by SPSS 25.0. Initially, normal distribution of the variables was analyzed by the Kolmogorov–Smimov test. Normally distributed data were analyzed by two-tailed Student's *t* test or one-way ANOVA. For non-parametric data, the Mann–Whitney *U* test was used for comparisons between groups. The differentiating diagnostic performances of all the variables with significant differences were assessed by values of the area under curve (AUC) obtained from the receiver operating characteristic

(ROC) curve. After post hoc analysis, the cutoff for abnormal score was determined by the value corresponding to maximal sum of sensitivity and specificity. However, since the number of PCACP without calcification was far less than PCACP with calcification, the propensity score matching (PSM) method was used to solve this problem by SPSS and R language plugin. After PSM, the paired data was analyzed again. A two-tailed p value of < 0.05 was considered statistically significant.

Results

Study population

A total of 49 patients with PCACP were enrolled in this study. Forty-two were with calcification and 7 were without calcification. Detailed demographic information of the study participants is presented in Supplementary Tables 1 and 2. The age of PCACP patients ranged from 1 to 14 years old, and their median age was 6 years old. The PCACP cohort consisted of 31 male (63.27%) and 18 female (36.73%).

Comparison of preoperative inflammatory markers, hormone markers, and radiological appearances between PCACP with and without calcification

As shown in Supplementary Table 1, significantly higher WBC, neutrophil, and monocyte counts were observed in PCACP patients with calcification than in patients without calcification. The PNI and PRL levels were observed to be higher in PCACP patients with calcification than in patients without it. The dNLR and PLR levels were observed to be higher in PCACP patients without calcification than in patients with calcification. In addition, the shape and T1WI signal of cysts also had significant difference between PCACP patients with and without calcification.

The inflammatory markers, hormone markers, and radiological appearances were further investigated according to PCACP's different kinds of calcification (Supplementary Table 2). There was not any significant difference between PCACP with point or slice calcification, PCACP with eggshell calcification, and PCACP with mixed calcification in quantity of calcification, maximum diameter of calcification and CCR (Supplementary Table 3).

Evaluation of the diagnosis efficacy for inflammatory markers, hormone markers, and radiological appearances in PCACP with and without calcification

The diagnostic values (ROC curves) were analyzed in this study. The corresponding AUC values appear in Supplementary Tables 4 and 5. The neutrophil count and PRL level demonstrated the highest accuracy in predicting PCACP with or without calcification (Fig. 1). Besides that, we also evaluated the markers for differentiating all kinds of PCACP calcification As shown in Supplementary Tables 4 and 5, ROC analysis indicated that NLR (AUC: 0.909; 95% CI 0.756–1.000), dNLR (AUC: 0.955; 95% CI 0.847–1.000), PLR (AUC: 0.909; 95% CI 0.756–1.000), MLR (AUC: 0.932; 95% CI 0.787–1.000), maximum diameter of cysts (AUC: 0.750; 95% CI 0.448–1.000), and classification of ACP (AUC: 0.886; 95% CI 0.700–1.000) had greater predictive value. The sensitivity, specificity, and cutoff of each marker are stated in Supplementary Tables 4 and 5.

Re-analyzed results after PSM

The most appropriate matching tolerance in this study was 0.5. After PSM, the number of pairs was 7. Coincidentally, significantly higher WBC, neutrophil, monocyte count, dNLR, and PRL level were also observed in PCACP patients with calcification than in patients without calcification. Besides that, NLR and MLR levels were observed to be higher in PCACP with calcification than in PCACP without calcification (Supplementary Table 6). Surprisingly, the AUC showed that neutrophil count (AUC: 0.990; 95% CI 0.950–1.000) and PRL level (AUC: 0.918; 95% CI 0.754–1.000) had greater predictive value for PCACP's calcification than before (Supplementary Table 7 and Fig. 2).

Discussion

CP represents one of the most frequently diagnosed hypothalamo-pituitary lesions in children [12, 13]. Though the most favorable management strategy for CP still has controversies, especially for PCACP, surgical gross total resection is generally considered the preferred curative method. Calcification of PCACP always tightly adheres to critical parasellar structure, increasing difficulty and injury rate in operation. Comparatively, the simple cyst of PCACP is more easily to be dealt with since its wall could indicate an obvious boundary between tumor and normal brain tissue. In addition, recent management of PCACP has shifted to focus on intracystic therapies by indwelling catheter to aspirate cystic fluid or to administrate special medicine [14–16]. Although this kind of treatment's curative effective is not definite, the multitudinous attempts hint that treating cystic component may be the breakthrough in managing PCACP. There have already been some studies about examining and reporting the specific ingredients of cystic fluid and calcification of ACP. However, their concrete formation mechanisms remain unknown [17–20]. Besides that, the shapes of calcification in PCACP are usually different, even sometimes absent. In our opinion, there may be multiple factors influencing

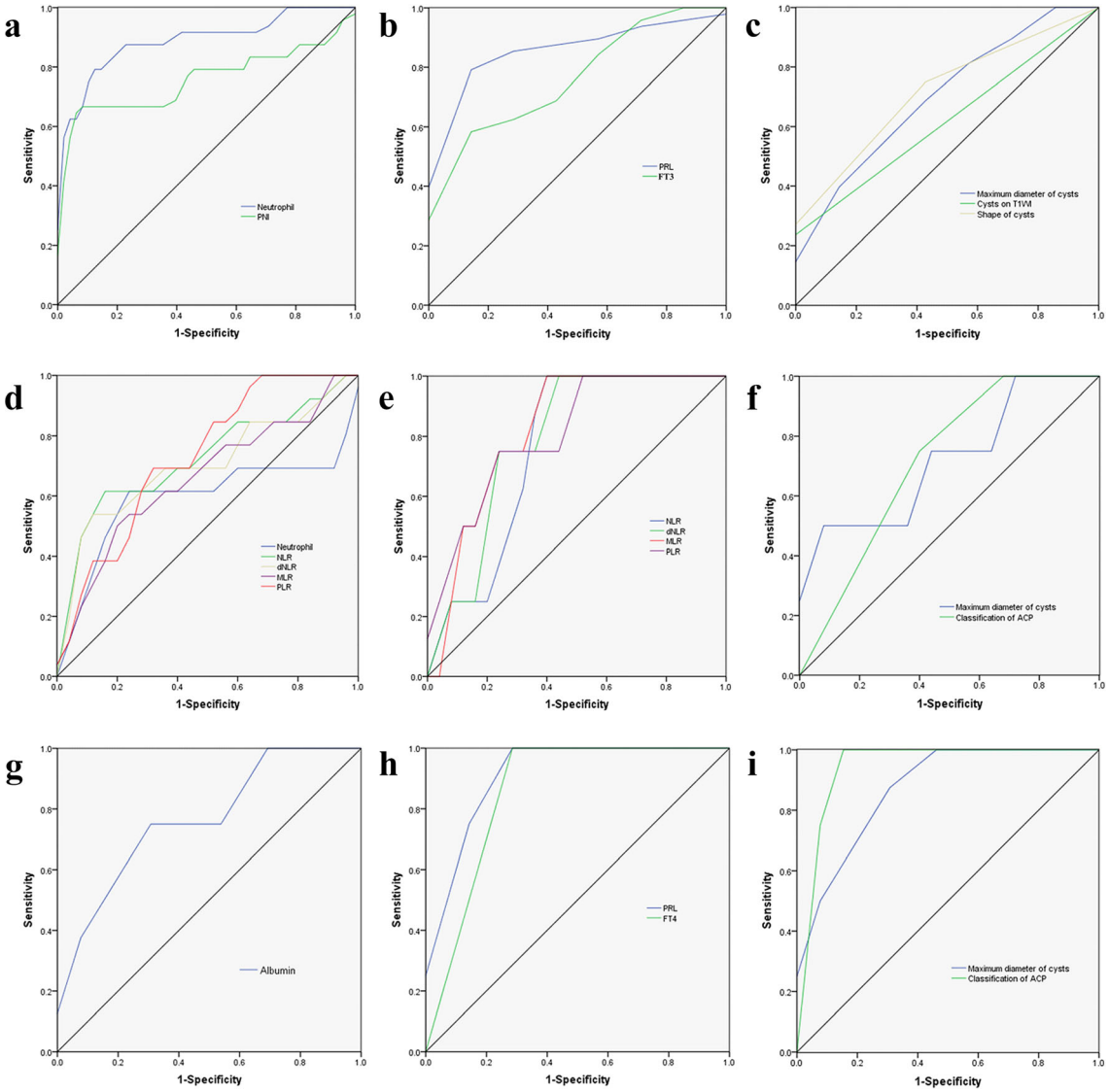

Fig. 1 Evaluation of the diagnosis efficacy for inflammatory markers, hormone markers, and radiological appearances in PCACP with and without calcification. The AUCs for neutrophil count, PNI, PRL, FT3, maximum diameter of cysts, cysts on T1WI and shape of cysts were higher than 0.7 between PCACP with and without calcification (**a**–**c**). The AUCs for neutrophil count, NLR, dNLR, MLR, and PLR were higher than 0.7 between PCACP with point or slice calcification and PCACP with eggshell calcification (**d**). The AUCs for NLR, dNLR, MLR, PLR, maximum diameter of cysts and classification of ACP were higher than 0.7 between PCACP with point or slice calcification and PCACP with mixed calcification (**e**, **f**). The AUCs for albumin, PRL, FT4, maximum diameter of cysts, and classification of ACP were higher than 0.7 between PCACP with eggshell calcification and PCACP with mixed calcification (**g**–**i**)

calcification formation in PCACP. Thus, in this study, we tried to use preoperative inflammatory markers, hormone markers, and radiological appearances to predict calcification tendency of PCACP.

Recent clinical and experimental studies have demonstrated that CP is correlated with inflammation [12, 18–27]. It was reported that inflammation from cystic fluid plays an important role in the development of ACP [18, 19]. WBC was found to be closely related to tumor cells' crucial biological characteristics [28, 29] and it was also associated with calcification in many diseases [30–34]. Results of this study indicated that the WBC, neutrophil, monocyte count, and PNI value were higher in PCAPC with calcification than in PCACP without calcification. All these conclusions above mean that calcification in PCACP could be associated with WBC. It has been reported that neutrophil-associated inflammatory factors in ACP cystic fluid such as IL-6, CXCL1, CXCL8, and TREM-1 were related to the development of CP [22–27, 35]. The neutrophil-defensins were detected in ACP fluid samples, showing a high expression in more than a half of cases [12, 18, 36]. In addition, the increase of neutrophil count was concerned with calcification in several diseases [32, 33]. These evidences mean that neutrophil could be relative to calcification formation in PCACP through regulating the

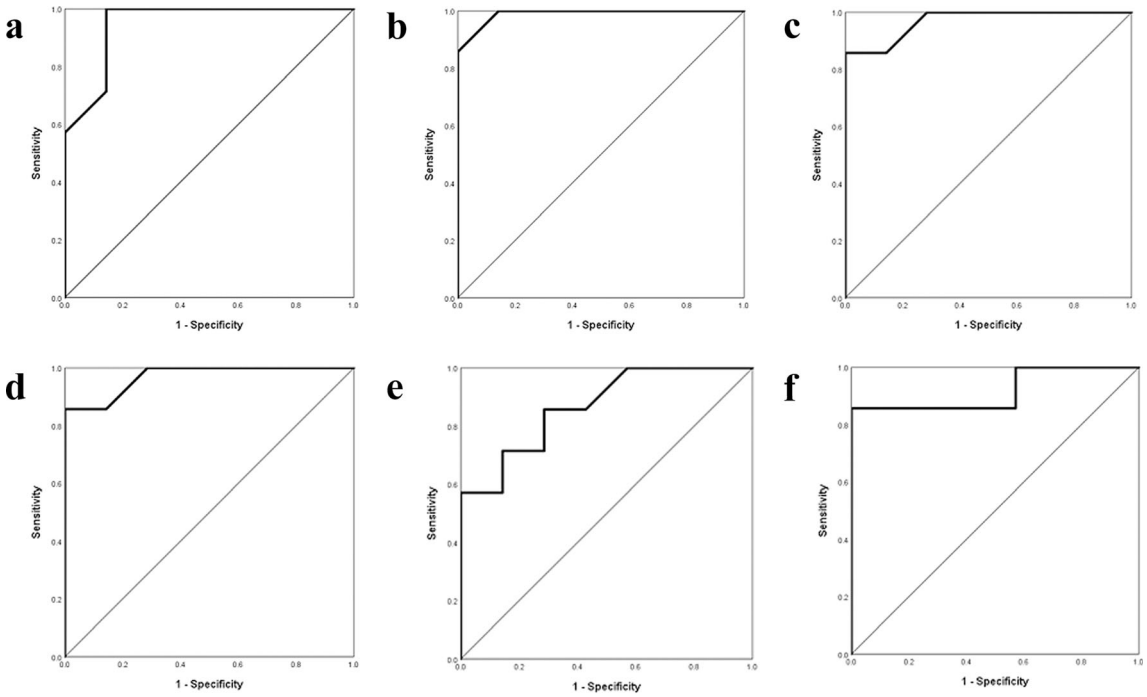

Fig. 2 Evaluation of the diagnosis efficacy for inflammatory markers, hormone markers, and radiological appearances in PCACP with and without calcification after PSM. The AUCs for WBC count, neutrophil count, NLR, dNLR, MLR, and PRL level were higher than 0.85 between PCACP with and without calcification. The AUC for WBC count was 0.949 (**a**). The AUC for neutrophil count was 0.990 (**b**). The AUC for NLR was 0.969 (**c**). The AUC for dNLR was 0.969 (**d**). The AUC for MLR was 0.867 (**e**). The AUC for PRL level was 0.918 (**f**)

micro-environment of cystic fluid. It was reported that macrophages could be recruited by a wide variety of factors secreted by tumor cells including IL-6, IL-10, and periostin in glioma [37, 38]. However, IL-6 and periostin were proved expressed in CP as well [22, 39]. This implies that monocyte could have similar way to influence PCACP's biological characteristics. Preoperative PNI is now widely used as parameters for nutritional status and systemic inflammatory response. Because of the chronic inflammation stimulation and the special relative position between CP and hypothalamus, the function of injured hypothalamus is often altered, especially in children, leading to the problem of energy management, decreased exercise, drowsiness, and eating disorder. The calcification of PCACP is tightly adhesive to hypothalamus, tending to lead to dysfunctions of hypothalamus and abnormal PNI level. The inflammatory markers of different PCACP's calcification forms were analyzed as well. The increasing WBC count means that severe inflammatory micro-environment could easily induce pure point or slice calcification in PCACP. On the other hand, the increasing neutrophil is helpful to induce pure eggshell calcification which is the special type in PCACP. These results hint that different inflammatory markers may cause different degrees of calcification.

Due to the special biological characteristic and location, CP often leads to hormone disorder. Abnormal hormone level caused by CP could influence both patients' general condition and tumor itself. Previous literatures reported that PRL promoted calcification in many diseases including tumor [40, 41]. It was generally known that PRL was closely related to pituitary prolactinoma. Some reports have showed that PRL may participate in the formation of calcification in prolactinoma by certain mechanisms [42–45]. In this study, the level of PRL was absolutely higher in PCACP with calcification than in PCACP without calcification. The PCACP with mixed calcification had the highest PRL level in all kinds of calcification types. These results all indicated that PRL could be related with calcification in PCACP.

The radiological appearances of cysts in PCACP with calcification were different to PCACP without calcification. The shape of cysts in PCACP with point or slice calcification tended to be irregular. PCACP with mixed calcification had the maximal diameter of cyst. The signal of cysts in PCACP with point or slice calcification was different from other groups and PCACP with eggshell calcification tended to be Id type CP according to its growth pattern. This series of findings indicated that the component and concentration of cystic fluid could be important to calcification of PCACP. The hyperintensive signal of cystic fluid stood for its possible complex components including high concentration of inflammatory factors, hormones, proteins, and other unknown substances. They may break the balance of secretion and absorption of cystic fluid in PCACP, consequently inducing calcium deposition. We guess that this process could be likely to the formation of gallstone in some ways. It was interesting that

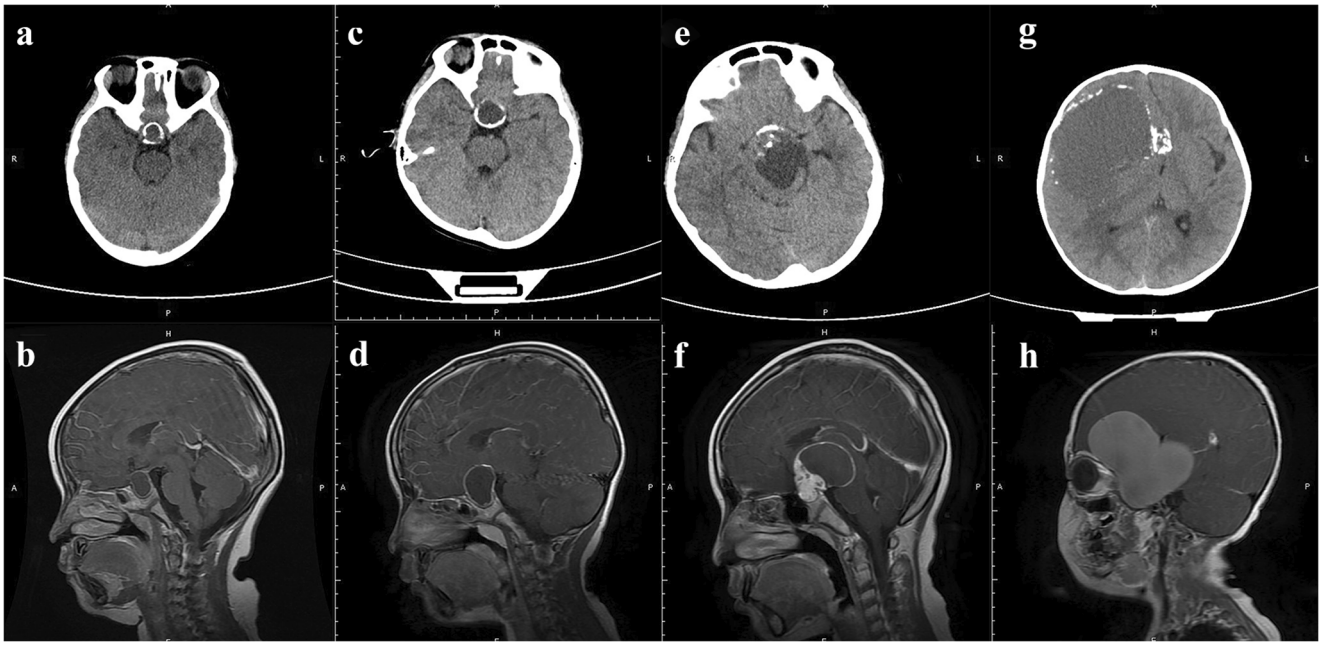

Fig. 3 Representative horizontal CT (**a**, **c**, **e**, **g**) and sagittal T1-weighted contrast-enhanced MRI (**b**, **d**, **f**, **h**) images in 2 PCACP patients with eggshell calcification and 2 PCACP patients with mixed calcification. Both **a** and **c** showed typical eggshell calcification in PCACP. Their corresponding MRI images (**b**, **d**) indicated the tumors originated from infradiaphragma. Retrospective analysis showed that the neutrophil count of these two cases was 9.2 and 4.52 (the average level was 2.23 ± 0.45, and the cutoff value was 2.745). The results matched our conclusion in this study. Similarly, both E and G showed mixed calcification in PCACP. Their corresponding MRI images (**f**, **h**) indicated the larger maximal diameters of PCACP cysts. Retrospective analysis showed that the PRL levels of these two cases were 298.88 and 1458.15 (the average level was 124.84 ± 119.65, and the cutoff value was 151.410). The results matched our conclusion in this study as well

both the calcification of PCAPC and gallstone were produced in cystic fluid environment and influenced by fluid components' imbalance. The cholesterol crystal ingredient both appeared in PCACP cystic fluid and gallstone calcification. Whether these two kinds of calcifications had the similar mechanism remained to be further studied and considered. In addition, the irregular shape and larger diameters of cysts meant the higher probability of greater volume calcification. The cysts originated and grew limitedly in infradiaphragma were more easily to formatting the special calcification shape of eggshell.

Most PCACP were with calcification, but there were still a number of cases without calcification. In our point of view, there might be some subtle differences in the components of cystic fluid between these two groups, so we assessed the performance of preoperative inflammation, hormone markers, and radiological appearances for exploring the differences between PCACP with and without calcification by ROC curve analysis. Only the neutrophil count and PRL level were higher than 0.8. This result matched the statistical outcome we mentioned before. The neutrophil count or PRL level in most PCACP with calcification was higher than 2.745×10^9/L or 126.281 mIU/L (Supplementary Table 8). Only 1 PCACP without calcification's neutrophil count was higher than its cutoff value, but its PRL level was lower than 126.281 mIU/L. However, since there was a large gap in quantity between PCACP with and without calcification, normal statistical analysis here may get biased results. In this study, we tried to use PSM method to solve this problem as far as possible. Surprisingly, the re-analysis showed almost the same results. The AUC value of neutrophil count and PRL level were even both greater than before. Besides that, the AUC value of inflammation-related markers including WBC count, NLR, dNLR, and MLR was all over 0.85. Therefore, we proposed that there might be some relationships between calcification formation and neutrophil count or PRL level in PCACP. High neutrophil count or PRL level may predict the calcification tendency in PCACP. Using medical inhibitors to reduce abnormally high neutrophil count or PRL level may help to decrease or slow down the formation of calcification in PCACP when Ommaya reservoir was implanted for intracystic therapies. If the tumor recurs, the operation will also benefit from less calcification adhesion. Moreover, combined with all the results, we found that the higher neutrophil count often indicated larger probability of tumor's Id growth pattern and special eggshell calcification. The higher PRL level always indicated tumor's larger size of cyst and mixed calcification (Fig. 3 and Supplementary Table 9). However, the specific reasons of these phenomena remained to be further studied.

There are still a few limitations in our study. First, our study consisted of a relatively small proportion of patients with

PCACP; in particular, only a limited number of PCACP patients without calcification were included. It was hard to avoid this problem even by using PSM method in this study. Thus, to avoid the selection bias, larger and multi-center studies are needed to confirm our preliminary results. Second, the results of preoperative inflammatory and hormone markers from peripheral blood samples are influenced by several factors such as the time, method, storage condition of blood collection, and test. However, other possible influence factors are still unknown. All these influence factors need to be eliminated in further studies. Third, the change of preoperative inflammatory markers' values that were observed in our study may be a reflection of a nonspecific inflammatory response due to PCACP. There is a risk of generating false-positive test results in screening asymptomatic populations. Hence, the roles of inflammatory markers, hormone markers, and radiological appearances should in PCACP be researched more deeply.

Conclusions

In conclusion, we found that inflammation and hormone are related to PCACP's calcification. High neutrophil count and PRL level may indicate possible calcification tendency in PCACP. Improved intracystic therapies based on these results may help to inhibit the formation of calcification in PCACP in future.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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