Comparison of relapsing polychondritis patients with and without central nervous system involvement: A retrospective study of 181 patients

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Abstract
The relapsing polychondritis (RP) patients with central nervous system (CNS) involvement were rare. We aimed to determine the clinical characteristics of RP patients with CNS involvement. The clinical data of 181 RP patients, hospitalized at Peking Union Medical College Hospital between December 2005 and February 2019, were collected. The patients were categorized into two subgroups: 25 RP patients with CNS involvement, and 156 RP patients without CNS involvement. The involvement of the ear was more frequent in RP patients with CNS involvement, compared with those of RP patients without CNS involvement (P < 0.01). After controlling sex and the admission age, logistic regression analysis revealed hypertension (odds ratio = 4.308, P = 0.006) and involvement of eye (odds ratio = 5.158, P = 0.001) and heart (odds ratio = 3.216, P = 0.025) were correlated with RP patients with CNS involvement, respectively. In addition, pulmonary infection (odds ratio = 0.170, P = 0.020), tracheal involvement (odds ratio = 0.073, P < 0.01), and involvement of laryngeal (odds ratio = 0.034, P = 0.001), costochondral joint (odds ratio = 0.311, P = 0.013), sternoclavicular joint (odds ratio = 0.163, P = 0.017) and manubriosternal joint (odds ratio = 0.171, P = 0.021) were associated with RP patients without CNS involvement, respectively. In contrast to RP patients without CNS involvement, the incidence of ear involvement was higher in RP patients with CNS involvement. After controlling the potential confounding factor sex and the admission age, hypertension and involvement of eye and heart were related with RP patients with CNS involvement, respectively.

Keywords
central nervous system, Chinese, neurological disorder, relapsing polychondritis

Date received: 4 January 2021; accepted: 9 February 2021

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Introduction

Relapsing polychondritis (RP) is a rare connective tissue disease involving multiple organs.\(^1\) A research from UK found that, the incidence of RP between 1990 and 2012 was 0.71 per million population per year.\(^2\) Another study revealed that there was a significant burden of disease on RP patients by analyzing patient-reported data.\(^3\) Horvath et al.\(^4\) conducted a epidemiology study of RP in Hungary, and demonstrated that the good survival rate of RP was possibly related with early diagnosis of the disease. The involvement of the central nervous system (CNS) in RP has occasionally been reported.\(^5,6\) Such CNS involvements can exhibit as meningitis, encephalitis, and meningoencephalitis.\(^7,8\) However, the pathogenesis of CNS involvement in RP remains unclear. Clinically, it is also unclear whether any clinical presentations or laboratory indexes are indicative of the occurrence of RP with CNS involvement. To the best of our knowledge, the clinical and laboratorial characteristics of RP patients with CNS involvement have not been compared with those of RP patients without CNS involvement. In the present study, we investigated the possible differences between these two RP subgroups. If the characteristic clinical spectrums of RP patients with CNS involvement were identified (e.g. onset features, involvement of other organs, other laboratory parameters), it would contribute greatly to earlier diagnosis of this subgroup of RP patients.

Materials and methods

This study was approved by the Ethics Committee of Peking Union Medical College Hospital. The written informed consent was obtained from all patients. We used the ICD code of RP to search all admissions to the Peking Union Medical College Hospital (PUMCH) from December 2005 to February 2019. A total of 201 patients had a definitive diagnosis of RP. The exclusive criteria were as follows: (a) RP overlapped with other immune-related diseases or with tumor; (b) the physicians were unable to determine whether the CNS disorders were caused by RP or other reasons. Two experienced rheumatologists participated in screening the clinical data and confirming the RP diagnosis. The diagnosis of RP was made using either the McAdam et al.’s\(^9\) criteria or diagnostic criteria introduced by Damiani and Levine.\(^10\) One exclusion criterion was that the diagnosis of RP overlapped with other immune-related diseases or with tumors, 17 patients met this exclusion criterion. Specifically, there were eight patients that overlapped with systemic vasculitis, one patient was associated with a common variable immunodeficiency disease, one patient overlapped with Sjögren’s syndrome, one patient overlapped with mixed connective tissue disease, two patients had complications with ankylosing spondylitis, two patients had complications with myelodysplastic syndrome, and two patients had complications with neoplasm (laryngocarcinoma in one case, esophagus cancer in the other case). Especially, among eight patients who overlapped with systemic vasculitis, five patients overlapped with GPA.

Two experts in the neurologic field were consulted to ensure the correct diagnosis of RP with CNS involvement. If these two neurological experts had any disagreements, another specialized neurologist was invited to resolve such disagreements. Three patients were further excluded due to difficulty in deciding whether the CNS disorders were induced by RP or other causes, such as atherosclerosis or age-related influences. Specifically, head MRIs showed ischemic changes in two middle-aged women. Multiple cerebral infarctions occurred in a 76-year-old man. The rest of the 181 patients were classified as RP with CNS involvement or RP without CNS involvement. After adequately ruling out other possible etiologies, such as infectious diseases, tumors, paraneoplastic syndrome, and adverse drug reactions, the diagnosis of RP with CNS involvement was established by clinical signs and symptoms, cerebrospinal fluid (CSF) examinations, cranial magnetic resonance imaging (MRI) findings, and treatment responses.\(^11\) Specifically, a diagnosis of autoimmune limbic encephalitis was made if the patient met the following four criteria: (1) subacute onset of working memory deficits, seizures, or psychiatric symptoms, suggesting involvement of the limbic system; (2) bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI that were highly restricted to the medial temporal lobes, or \(^{18}\)fluorodeoxyglucose (\(^{18}\)F-FDG) positron emission tomography (PET) showing a decrease in FDG uptake in medial temporal lobes; (3) a CSF white blood cell (WBC) count of more than five cells per mm\(^3\), or an electroencephalogram (EEG) with epileptic or slow-wave activity involving the temporal lobes; and (4) reasonable exclusion of alternative causes, such as herpes simplex virus encephalitis, HHV-6 encephalitis, glioma, status epilepticus, neurosyphilis, Whipple, human immunodeficiency virus.\(^12\) Two of the five patients with autoimmune limbic encephalitis were
tested for anti–glutamic acid decarboxylase (GAD), anti–N-methyl-D-aspartate receptor (NMDAR), anti-Hu, anti-Yo, and anti-Ri antibody. The result was negative. Meningitis was defined by headache, nuchal rigidity, combined with the increased CSF pressure, elevated number of WBC or protein in the CSF. If the patient manifested as abnormal brain function, radiographic lesions detected in cranial MRI, and increased CSF WBC count or protein concentration, then a diagnosis of encephalitis in addition to autoimmune limbic encephalitis was established. The diagnosis of myelitis was based on typical clinical symptoms/signs in combination with abnormal MRI signals in the spinal cord. The diagnosis of the involvement of optic nerve was based on ophthalmologic symptoms, signs, orbital MRI, examination of ocular fundus, and joint evaluation of neurologist and ophthalmologist. Of note, one patient presented with a severe headache, nausea, and projectile vomiting, which is a combination of symptoms that is similar to that of intracranial hypertension. After ruling out other etiologies, such as intracranial mass lesion or infection, RP with CNS involvement was suspected. In the case, methylprednisolone (1 g) was administered for 3 days, during which symptoms were completely remitted. Hence, the patient was diagnosed with a CNS disorder. Finally, 25 RP patients were confirmed to have CNS lesions. The other 156 patients were categorized as RP without CNS involvement. Manifestations of cardiac involvement via routine electrocardiograms and echocardiogram included aortic valve incompetence, aortic aneurysm, mitral regurgitation, aortic or mitral valve thickening, aortic root dilatation, pericarditis, and right-bundle branch blockage. The keratoconjunctivitis was included in the involvement of eye in the study.

Neurological presentations of RP, such as aseptic meningitis, encephalitis, meningoencephalitis, and cranial nerve palsy, have previously been reported. If the RP patients with CNS involvement in our study had two or more forms of neurological involvement, they were classified as overlapping nervous-system involvement. Otherwise, the other patients were considered to have only a single nervous system involvement. Involvement of the peripheral nervous system (e.g., cranial nerve palsy excluding the optic nerve and olfactory nerve) was diagnosed according to clinical symptoms, signs, electromyography, and evaluation by expert neuropathologists. We also performed a preliminary investigation of the RP patients with overlapping or single nervous-system involvements. Due to the risk of invasive operation, the nerve biopsy was not performed.

**Statistical analysis**

We used the Statistical Package for the Social Sciences (version 24.0; IBM Corp., Armonk, NY, USA) to perform all statistical analyses. If a dataset was not normally distributed, the Mann–Whitney rank sum test was performed for comparing the difference between groups. Normally distributed datasets with homogeneities of variance were compared by unpaired Student’s $t$ tests. Qualitative data were compared using $\chi^2$ tests or Fisher exact test. The univariate analysis was used to compare the difference between RP patients with CNS involvement and those without CNS involvement. In the final logistic regression model, the significant variables from the univariate analysis were included separately, in a enter process. The potential confounding factors sex and age on admission were also controlled to identify the association between clinical parameters and RP patients with CNS involvement. A $P$-value less than 0.05 was regarded as statistically significant.

**Results**

**The characteristics of RP with CNS involvement**

There were 201 RP patients hospitalized at PUMCH between December 2005 and February 2019. A total of 20 patients were excluded, as noted in the materials and methods section above. Hence, 181 patients were included in the present study, among which 25 patients were classified as RP with CNS disorder. During the same period, the percentage of RP patients with CNS involvement among hospitalized RP patients was 13.81% (25/181). As shown in Supplementary Table 1, RP patients with CNS involvement were 32–79 years old (mean = 51.28 years old). As demonstrated in Table 1, the diagnosis of limbic encephalitis was validated in five patients (cases 5, 14, 16, 18, and 21). In cases 14 and 21, EEGs revealed slow-wave activity involving the temporal lobes. Pleocytosis were observed in 14 patients. There were 11 patients with decreased CSF chlorides. The majority of patients displayed lymphocytic inflammation in terms of CSF cytology. In terms of treatment, two patients were administered with a recombinant human tumor necrosis factor receptor type-II antibody fusion protein and an IL-6...
receptor antagonist, respectively. Intravenous methylprednisolone pulse therapy (1 g for 3 days) was prescribed in nine patients. Intravenous immune globulin and immunosuppressive therapy (cyclophosphamide, mycophenolate mofetil, methotrexate, tripterygium glycosides, and cyclosporin A) were also added to help control the disease.

**Comparison of RP patients with overlapping nervous-system involvement and those with single nervous-system involvement**

There were ten patients with encephalitis, six patients with aseptic meningitis, six patients with meningoencephalitis, and two patients with myelitis. Encephalitis (40.00%) was the most common manifestation of CNS involvement, followed by aseptic meningitis (24.00%) and meningoencephalitis (24.00%).

Among the 25 patients with CNS disorders, 11 patients had overlapping neurological involvements, and 14 patients had single neurological involvements. Compared with those of RP patients with single neurological involvements, the frequencies of smoking and drinking histories were higher in RP patients with overlapping neurological involvement ($P=0.049$, $P=0.026$, respectively; Table 2). There was no difference in terms of organ involvement (Table 2).

**Comparison of RP with and without CNS involvement**

Among 156 RP patients without CNS involvement, the ratio of females to males was 0.86: 1. The average age on admission was 46.17 years. No sex or disease duration differences were found between RP patients with CNS involvement and those

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**Table 1.** Clinical data of 25 relapsing polychondritis patients with central-nervous-system involvement.

| Case | Diagnosis | CSF pressure (mmHg) | CSF WBC ($10^6$/L) | CSF protein* (g/L) |
|------|-----------|---------------------|---------------------|--------------------|
| 1    | Meningoencephalitis | >330 | 90 | 0.51 |
| 2    | Meningoencephalitis | 205 | 500 | 1.81 |
| 3    | Meningoencephalitis | 310 | 96 | 0.99 |
| 4    | Aseptic meningitis + involvement of bilateral oculomotor nerves | 180 | 2 | 0.97 |
| 5    | Limbic encephalitis + myelitis | 190 | 12 | 0.47 |
| 6    | Encephalitis + involvement of VII, IX, X, and XII cranial nerves | 65 | 202 | 0.77 |
| 7    | Meningoencephalitis + incomplete dorsolateral medullary syndrome + injury of V and VII cranial nerves | 180 | 30 | 0.66 |
| 8    | Aseptic meningitis + involvement of III and VI cranial nerves | 300 | 70 | 0.737 |
| 9    | Acute encephalomyelitis | 110 | 8 | 0.58 |
| 10   | Meningoencephalitis | 310 | 4 | 0.619 |
| 11   | Meningoencephalitis | 210 | 42 | 0.75 |
| 12   | Encephalitis | 180 | 0 | 0.49 |
| 13   | Aseptic meningitis | 285 | 0 | 0.5 |
| 14   | Limbic encephalitis | 130 | 0 | 0.55 |
| 15   | Aseptic meningitis | 270 | 713 | 0.61 |
| 16   | Limbic encephalitis | 180 | 12 | 0.49 |
| 17   | Aseptic meningitis | >330 | 56 | 0.57 |
| 18   | Limbic encephalitis | 270 | 1 | 0.24 |
| 19   | Manifestation similar with intracranial hypertension | 91 | 0 | 0.27 |
| 20   | Encephalitis | 165 | 80 | 0.86 |
| 21   | Limbic encephalitis | 145 | 0 | 0.48 |
| 22   | Aseptic meningitis | 230 | 12 | 0.28 |
| 23   | Encephalitis | 140 | 3 | 0.56 |
| 24   | The involvement of optic nerve | | | |
| 25   | The involvement of optic nerve | | | |

CSF: cerebrospinal fluid; WBC: white blood cell.

*CSF protein: the normal range of cerebrospinal fluid protein was 0.15–0.45 g/L.
without CNS involvement (Table 3). The admission age was older in RP patients with CNS involvement in contrast to those without CNS involvement ($P=0.046$). In terms of comorbidities, RP patients with CNS involvement had a higher percentage of hypertension ($P=0.001$) and a lower percentage of pulmonary infection ($P=0.021$). There was no statistically significant difference between the two subgroups in terms of diabetes.

With respect to clinical presentations, the incidences of involvements of the eyes, heart and peripheral nerve system in RP patients with CNS involvement were significantly higher than those in RP patients without CNS involvement ($P<0.01$, $P=0.009$, $P=0.023$, respectively; Table 3). Additionally, the incidences of laryngeal, tracheobronchial tree, costochondral, sternoclavicular, and manubriosternal articulation involvements in RP patients with CNS involvement were lower as compared with those of the RP patients without CNS involvement ($P=0.001$, $P<0.01$, $P=0.006$, $P=0.010$, $P=0.011$, respectively; Table 3). Particularly, the involvement of ear occurred in all of the 25 RP patients with CNS involvement. In the subgroup of RP patients without CNS involvement, 88 of 156 patients had the involvement of ear. The result of Fisher exact test showed the difference in incidence of ear involvement between these two groups was statistically significant ($P<0.01$).

In regard to laboratory tests, there were no significant differences in erythrocyte sediment rate, C-reactive protein, WBC count, or the absolute number of neutrophils or lymphocytes (Table 3). The abovementioned statistically significant variables from the univariate analysis were included separately in the final logistic regression analysis. Each model consisted of three independent variables, and the sex and admission age were used as

Table 2. Comparisons between relapsing polychondritis patients with overlapping/single nervous system involvement.

|                      | RP with overlapping neurological disorder (N=11) | RP with single neurological disorder (N=14) | $P$ value |
|----------------------|-----------------------------------------------|---------------------------------------------|-----------|
|                      | $n$ (%)/mean ± SD/median ± IQR                 | $n$ (%)/mean ± SD/median ± IQR               |           |
| Male                 | 7 (63.64) 49.55 ± 15.04 6.00 ± 10.00          | 9 (64.29) 52.64 ± 13.84 6.50 ± 17.25         | 1.000     |
| Age on admission     | 10.00 ± 12.00                                 | 5.00 ± 10.00                                | 0.598     |
| Course of disease (month) | 5.00 ± 10.00                               | 6.00 ± 8.50                                | 0.936     |
| Diagnosis delay time (month) | 7 (63.64) 3 (21.43)                        | 3 (21.43)                                  | 0.049*    |
| History of smoking   | 5 (45.45) 4 (28.57)                           | 4 (28.57)                                  | 0.434     |
| Pulmonary infection   | 0 (0) 2 (14.29)                               | 2 (14.29)                                  | 0.487     |
| Diabetes             | 3 (27.27)                                    | 7 (50.00)                                  | 0.661     |
| Weak                 | 5 (45.45) 6 (42.86)                           | 7 (50.00)                                  | 1.000     |
| Loss of weight       | 4 (36.36)                                    | 6 (42.86)                                  | 1.000     |
| Ocular involvement   | 8 (72.73)                                    | 10 (71.43)                                 | 1.000     |
| Involvement of laryngeal | 0 (0)                                      | 1 (7.14)                                   | 1.000     |
| Tracheal involvement | 2 (18.18)                                    | 5 (35.71)                                  | 0.407     |
| Involvement of costochondral joint | 3 (27.27)                                   | 5 (35.71)                                  | 1.000     |
| Involvement of sternoclavicular joint | 0 (0)                                      | 2 (14.29)                                  | 0.487     |
| Involvement of manubriosternal joint | 0 (0)                                      | 2 (14.29)                                  | 0.487     |
| Involvement of nose  | 6 (54.55)                                    | 8 (57.14)                                  | 1.000     |
| Cutaneous involvement| 2 (18.18)                                    | 5 (35.71)                                  | 0.407     |
| Erythrocyte sedimentation rate | 50.91 ± 43.10                              | 55.07 ± 44.78                               | 0.817     |
| C-reactive protein   | 36.17 ± 49.46                                 | 30.54 ± 83.9                                | 0.687     |
| White blood cell     | 8.3 ± 4.31                                    | 10.30 ± 5.00                                | 1.000     |
| Absolute value of lymphocyte | 1.72 ± 0.53                                 | 1.65 ± 1.00                                 | 0.838     |
| Absolute value of neutrophil | 6.79 ± 3.97                                 | 7.87 ± 4.25                                 | 1.000     |
| Hemoglobin           | 132.27 ± 21.68                                | 117 ± 19.62                                 | 0.078     |
| Platelet             | 351 ± 184                                    | 262.36 ± 106.66                             | 0.373     |

RP: relapsing polychondritis; SD: standard deviation; IQR: interquartile range.

*P < 0.05.
controlled variables in the regression model. The results (Table 4) revealed hypertension (odds ratio = 4.308, \( P = 0.006 \)) and involvement of eye (odds ratio = 5.158, \( P = 0.001 \)) and heart (odds ratio = 3.216, \( P = 0.025 \)) were associated with RP patients with CNS involvement, respectively. While pulmonary infection (odds ratio = 0.170, \( P = 0.020 \)), tracheal involvement (odds ratio = 0.073, \( P < 0.01 \)), and involvement of laryngeal (odds ratio = 0.034, \( P = 0.001 \)), costochondral joint (odds ratio = 0.311, \( P = 0.013 \)), sternoclavicular joint (odds ratio = 0.163, \( P = 0.017 \)) and manubriosternal joint (odds ratio = 0.171, \( P = 0.021 \)) were related with RP patients without CNS involvement, respectively.

Discussion

RP is characterized by an extensive inflammatory affection of the cartilage, ears, nose, airway, eyes, larynx, kidneys, and heart.\(^1\) Intercurrent
rheumatologic diseases, solid tumors, hematologic malignancies, and myelodysplastic syndrome have been shown to also be present in RP patients.\textsuperscript{8,13,14} These associated disorders may have biased our comparative results between the two subgroups in the present study. Hence, we excluded any RP patients with these related diseases from analyses in the present study.

Trentham and Le\textsuperscript{15} investigated 36 RP patients and found that 3\% of these RP patients exhibited neurologic manifestations. Additionally, Zeuner et al.\textsuperscript{16} described clinical findings from 62 RP patients and found that 9.7\% of these RP patients exhibited CNS involvement. Recently, a study from France included 142 RP patients and demonstrated CNS involvement occurred in 8\% of these patients.\textsuperscript{14} In the present study, our data showed that up to 13.81\% of Chinese RP patients exhibited CNS involvement. This finding suggests that CNS involvement in RP is not less common in China. After excluding other possible causes of neurologic disorders in RP patients, our findings highlight that continued awareness of CNS involvement in RP is important in clinical practice. In terms of CSF tests, our study indicated that the majority of patients presented with elevated intracranial pressure and protein, reduced chlorides, and lymphocytic inflammation. The above CSF results corroborated similar findings from previous studies,\textsuperscript{6,17} which suggests that intracranial inflammation may contribute to clinical diagnosis of RP with CNS involvement.

Our present study found that not only encephalitis was the most common CNS manifestation in RP patients, but also the CNS manifestations were considerably heterogeneous. Importantly, our study revealed that CNS disorders frequently accompany peripheral-nervous-system lesions concurrently.

In the present study, a high prevalence of hypertension was observed in RP patients with CNS involvement, compared to that of RP patients without CNS involvement. After controlling the influence of sex and the admission age, the logistic regression analysis showed that hypertension was correlated with RP patients with CNS involvement. Moreover, there were higher frequencies of smoking and drinking histories in RP patients with overlapping neurological involvement, compared to those of RP patients with only a single neurological involvement. Pallo et al.\textsuperscript{18} reported that RP patients had higher prevalence of arterial hypertension and diabetes mellitus (DB), as compared to those in matched healthy individuals. The correlation of arterial hypertension and DB with RP was further confirmed by multivariate analysis. Previous studies have revealed that in other inflammatory rheumatic diseases, such as rheumatoid arthritis, systematic lupus erythematosus, psoriatic arthritis, and polymyositis, smoking exposure may increase the risk of disease morbidity.\textsuperscript{19-22} We found that hypertension may be associated with CNS involvement in RP patients. Additionally, exposure to smoking and alcohol may be related to extensive neurological involvement in RP patients. As such, controlling hypertension, quitting cigarette smoking, and stopping alcohol consumption may represent promising therapeutic interventions for avoiding CNS involvement in RP patients. This hypothesis will require further validation via future epidemiological studies and larger scale case-controlled studies.

\begin{table}
\centering
\caption{Clinical indexes associated with relapsing polychondritis patients with central nervous system involvement (potential confounding factors sex and age on admission were controlled).}
\begin{tabular}{|l|c|c|}
\hline
 & Odds ratio & \textit{P} value \\
\hline
e & 4.308 (1.532–12.118) & 0.006 \\
e & 0.170 (0.038–0.753) & 0.020 \\
e & 5.158 (2.000–13.301) & 0.001 \\
e & 0.073 (0.027–0.197) & \textless 0.01 \\
e & 0.034 (0.004–0.257) & 0.001 \\
e & 0.311 (0.124–0.779) & 0.013 \\
e & 0.163 (0.037–0.724) & 0.017 \\
e & 0.171 (0.038–0.767) & 0.021 \\
e & 3.963 (0.993–15.816) & 0.051 \\
e & 3.216 (1.162–8.900) & 0.025 \\
\hline
\end{tabular}
\end{table}

\*Cardiac involvement: There were 3 and 39 missing values in relapsing polychondritis patients with central nervous system involvement and those without central nervous system involvement, respectively. The logistic regression analysis was performed after excluding the missing values.
To the best of our knowledge, the present study represented the first explicit comparison of RP patients with CNS involvement and RP patients without CNS involvement. The frequency of laryngeal and tracheobronchial tree involvement was more common in RP patients without CNS involvement. Accordingly, the rate of pulmonary infection was higher in this subgroup. This finding is consistent from the perspective of experiences in clinical practice.

CNS complications are more common in RP patients with cardiac involvement. Using correlation matrix analysis, Shimizu et al. observed positive relationships among cardiovascular, external ear, and neurological involvement in Japanese patients with RP. The positive association between internal ear involvement and eye involvement was also found. In addition, they discovered a correlation between airway involvement (laryngeal and tracheobronchial) and external ear involvement, and airway involvement and neurological involvement were inversely correlated. The clinical analysis of subgroups in Japanese patients with RP revealed that auricular involvement frequently occurred with CNS involvement. The cardiovascular involvement was not found in the subgroup of patients with respiratory involvement. An inverse correlation between auricular and tracheobronchial involvements was observed in French patients with RP. Our present research results and the above-mentioned research findings in Japan and France were mutually confirmed and suggested close connections between organ involvement in RP patients.

Our study indicated that the incidence of ear involvement is higher in RP patients with CNS patient. We further probed into the possible reasons. On one hand, vasculitis may be important for CNS involving following RP. The pathology of CNS lesions in RP patients was thought to be common, that is, inflammation of CNS. Recently, Matsuzono et al. reported the first case that RP coupling with an amyloid deposit induced the cerebral amyloid angiopathy-related inflammation (CAARI). The autoimmune inflammation related to an amyloid deposit was considered to be the important factor of CAARI. Meanwhile, the pathology of auricular cartilage showed the infiltration of lymphocytes and neutrophils. We speculated, the ear and CNS involvements in RP patients may share the common pathological mechanism-inflammation. On the other hand, we speculated inflammation was severe in the ear involvement cases. Kuwabara et al. first reported auricular hyperintensity on diffusion-weighted magnetic resonance imaging (DWI) in a RP patient with encephalitis. The histopathological examination of auricle revealed infiltration of inflammatory cells in the perichondrium, which was consistent with the characteristic MR imaging finding. They named the MR finding “prominent ear sign.” The prominent ear sign demonstrated the ear inflammation activity. This study suggested that the ear inflammation may be prominent in RP patients with CNS vasculitis or meningoencephalitis.

Additionally, our present study provided new insights into the associations of organ involvement with RP patients with CNS involvement. We revealed that ocular involvement was correlated with CNS involvement in RP patients. We also found costochondral, sternoclavicular, and manubriosternal joint involvement was associated with RP patients without CNS involvement. Notably, cardiac abnormalities/complications in RP were considered to portend a poor prognosis. Hence, we speculate that CNS involvement of RP may reflect the severity of RP.

Several mechanisms of CNS involvement of RP have been proposed. Antibodies against type-2 collagen, glutamate receptor epsilon 2, and neutral glycosphingolipids were present in RP patients with limbic encephalitis. Moreover, an increasing body of evidence has revealed pathological presentations of vasculitis and inflammatory changes—such as T-cell infiltration, panencephalitis, and granuloma formation—in RP patients. In our study, the incidence of ear involvement was higher in RP patients with CNS involvement compared with RP patients without CNS involvement. The involvement of the eyes and heart was correlated with RP patients with CNS involvement, after the factors sex and the admission age were controlled. In contrast to RP patients without CNS involvement, the incidence of ear involvement was higher in RP patients with CNS involvement. We speculate that, to some extent, this phenomenon systematically reflected the presence of serious inflammatory reactions in RP patients with CNS involvement.

There were some limitations in the study. Firstly, it is retrospective. A prospective study on RP patients is warranted in the future. Secondly, the
power calculation was not done for estimation of sample size selected for the study. Finally, due to the high number of statistical tests, the interpretation of results close to the 0.05 cut-off should be cautious.

Conclusions
All in all, our investigation revealed that RP patients with CNS involvement can present with varying clinical features. Among these manifestations, encephalitis was the most common one. The occurrence of RP patients with overlapping neurological presentations may be correlated with increased exposure to smoking and alcohol consumption. RP with CNS involvement was more likely to be found in patients with ear involvement. After controlling the potential confounding factor sex and the admission age, hypertension and involvement of eye and heart were associated with RP patients with CNS involvement, respectively. Furthermore, pulmonary infection, tracheobronchial tree involvement, and involvement of laryngeal, costochondral joint, sternoclavicular joint, and manubriosternal joint were associated with RP patients without CNS involvement, respectively.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval
Ethical approval for this study was obtained from The Ethics Committee of Peking Union Medical College Hospital. The approval number was JS-2038.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China [grant number:81671614, the website: www.nsfc.gov.cn/]; Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) [grant number:2017-12M-3-001]; and the National Key Research and Development Program of China (grant number: No. 2016YFC0901500).

Informed consent
Written informed consent was obtained from all subjects before the study.

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Supplemental material
Supplemental material for this article is available online.

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