The analysis of mirror pattern bands synthesized in patients with neurological disorder during Oligoclonal immunoglobulin isoelectric focusing electrophoresis

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Abstract

Background

The analysis of oligoclonal band (OCB) of cerebrospinal fluid is of vital importance for the clinical diagnosis and differential diagnosis of neurological disease. However, there still exists limited knowledge about the interpretation for the OCB patterns especially the mirror patterns for the neurological disorder during the clinical course. In this study, we thoroughly analyzed the 12 patients of mirror pattern results with laboratory and clinical information.

Methods

Specimens were obtained from patients who had CSF and serum analyzed by isoelectric focusing (IEF) in the Special Examination Laboratory of XuanWu Hospital over a 4-year period. 12 patients with mirror patterns were screened out by isoelectric focusing electrophoresis from 5892 patients and then immunofixation electrophoresis were performed on the 12 patients.

Results

All three types of mirror patterns are closely connected with M protein from peripheral serum. However, not all patients with the mirror patterns present positive M protein. 7 out of 12 patients (58.3%) patients were diagnosed as blood system-related diseases. None of the 12 patients were diagnosed with Multiple Sclerosis.

Conclusions

Great emphasis should be taken on the mirror pattern during the isoelectric focusing electrophoresis. The mirror pattern combined with the result of M protein will contributes to the differential diagnosis of neurological disorder.

Background

Oligoclonal Bands (OCB) is the most consistent and characteristic features of Multiple Sclerosis (MS) [1]. Intrathecal oligoclonal band synthesis occurs in over 90% of patients with clinically definite MS but may also occur in the context of CNS infection and other inflammatory conditions [2]. The isoelectric focusing (IEF) on agarose gels followed by immunoblotting has been universally recognized as the “gold standard” for detecting the presence of oligoclonal bands. [3-5] ADDIN EN.CITE OCB
serves as not only an especially valuable tool for differential diagnosis but also for prognosis [6] ADDIN EN.CITE , and even for predicting the conversion of optic neuritis and clinically isolated syndromes (CIS) to MS[7]. For such a qualitative and clinically significant technique, the correct recognition and interpretation of CSF oligoclonal band patterns is utmost crucial. A general consensus is that there are five typical types of band patterns [8] ADDIN EN.CITE , of which the presence of oligoclonal bands in CSF but not in serum means local synthesis of immunoglobins in the central nervous system, which is most likely observed in patients with MS [8, 9] ADDIN EN.CITE . Relatively little attention has been paid, however, to the mirror patterns, which are quite uncommon and the clinical significance is still rarely clarified. There are three types of abnormal mirror patterns, the first type is termed “type 3”, which performs both identical bands in CSF and serum and additional CSF restricted oligoclonal bands. The second is so-called “type 4”, which presents identical oligoclonal bands (irregularly spaced bands) in CSF and serum, and indicates a systemic instead of intrathecal immune reaction[4]. The third type is “type 5”, which symmetrically displays monoclonal bands both in the CSF and serum sample[10]. The monoclonal bands have the characteristic of space in symmetric steps among bands and tend to be evenly distributed [11, 12] ADDIN EN.CITE . The monoclonal proteins form clusters and are more prominent, with higher concentrations and stronger immunoreaction, which actually makes this band patterns more easier to recognize[13]. This identical multiple bands in both CSF and serum (mirror pattern) may be relative to the following disorders, such as the systemic inflammation, probable MS, systemic lupus erythematosus, paraneoplastic syndrome, vascular disease, peripheral neuropathies and so on [2, 11, 14] ADDIN EN.CITE . However, in clinical practice, there are still many discrepancies among different research institution in interpreting the above three CSF/serum mirror patterns, which is to a large extent attribute to the very rare occurrence [15] ADDIN EN.CITE . Quite a few neurologists usually unreasonably downplayed the clinical significance of mirror patterns when the paired CSF and serum samples were analyzed for OCB, instead played more emphasis on the classical pattern 2 which to a large extent indicates MS. CSF analysis is undoubtedly an important tool for diagnosis for those with neurological disorders [16, 17] ADDIN EN.CITE . Analysis of paired CSF/serum for OCB has been a conventional laboratory method
in our laboratory for the patients with neurological dysfunction but without clear pathogeny. In the past four years, among 5892 patients who received OCB detection in our hospital, just only 12 cases presented the mirror patterns. In this study, we focus on the 12 patients with comprehensive clinical and laboratory information in order to further evaluate the potential value of OCB mirror patterns and to what extent OCB mirror patterns results influence the final diagnosis.

Results

1. The demographical and immunological data of the 12 patients with mirror patterns are summarized in Table 1. Oligoclonal IgG band results of all the 12 patients accompanied with immunofixation electrophoresis respectively are shown in the Figure 1. Five patients were female and seven patients were male. The mean age were 59.5 years (range 42-72). A quantitative measured increased intrathecal synthesis of IgG was present in 5 patients (No. 1,3,5,11,12) and was always accompanied by the increased QALB. Expect for three patients (No.4,5,9), the other nine patients were positive for M protein. Besides, among 12 cases with mirror patterns, only one patient (No. 5) presented pattern 3 (a mirror plus pattern), two patients displayed pattern 4 (equal number of matched bands in CSF and serum) and nine patients presented pattern 5 (monoclonal bands).

2. The clinical characteristics of all the 12 patients are presented in Table 2 including the first clinical symptoms and the final diagnosis. 8 out of 12 cases (patient No.1,2,3,4,5,7,8,11) were at the onset of atypical demyelinating lesion of peripheral nervous system. 7 patients (No.1,2,3,7,8,11,12) were finally diagnosed as blood system-related diseases including MM, POEMS, and MGUS.
Table 2. Overview of the clinical characteristics of 12 patients

| No. | Gender | Age | CSF TP (mg/dl) | QALB ($\times 10^3$) | C-IgG (mg/dl) | S-IgG (mg/dl) | OCB patterns |
|-----|--------|-----|----------------|----------------------|--------------|--------------|--------------|
| 1   | Female | 62  | 141            | 20.9                 | 37.9         | 3160         | P5           |
| 2   | Male   | 53  | 56             | 9.1                  | 4.95         | 1040         | P5           |
| 3   | Female | 62  | 181            | 37                   | 35.2         | 1200         | P5           |
| 4   | Male   | 55  | 39             | 7                    | 7.53         | 1260         | P5           |
| 5   | Male   | 68  | 123            | 24                   | 13.9         | 1040         | P3           |
| 6   | Female | 53  | 64             | 9.8                  | 7.06         | 1860         | P4           |
| 7   | Female | 42  | 21             | 3.3                  | 2.66         | 1160         | P5           |
| 8   | Male   | 69  | 30             | 4.2                  | 2.78         | 1300         | P5           |
| 9   | Male   | 72  | 41             | 6.4                  | 4.33         | 1280         | P5           |
| 10  | Male   | 65  | 49             | 6.5                  | 4.46         | 1450         | P5           |
| 11  | Male   | 59  | 173            | 38                   | 45.1         | 1990         | P4           |
| 12  | Female | 54  | 94             | 12.6                 | 18.3         | 2130         | P5           |

NO.: patient number, Age: patient age in years, CSF: cerebrospinal fluid, TP: total protein, OCB: oligoclonal bands, QALB: CSF/serum albumin quotient, IgG-Syn: intrathecal IgG synthesis, C-IgG: CSF IgG, S-IgG: Serum IgG, MS: multiple sclerosis, SIE: serum immunofixation electrophoresis, P3: pattern 3, P4: pattern 4, P5: pattern 5, ND: not detected.
| No. | First and primary clinical manifestation | Confirmed diagnosis |
|-----|-----------------------------------------|---------------------|
| 1   | Numbness and weakness of both lower limbs for 2 years | MM |
| 2   | Burning sensation on both feet for half a year | POEMS |
| 3   | Numbness and weakness of both lower limbs for two years, walking unsteadily for a month | MGUS |
| 4   | Progressive muscle weakness of lower limbs for 2 years | ALS |
| 5   | Numbness and weakness of both lower limbs for 53 days | IMID |
| 6   | Paroxysmal consciousness disorder with limb stiffness for 18 days | Viral encephalitis? |
| 7   | Numbness and weakness of both lower limbs for 5 months | 1Demyelinating myelopathy 2MGAPU 3MGUS |
| 8   | Cold sensation on both lower limbs for 3 years, walking unsteadily for 1.5 years | MGUS |
| 9   | Memory loss for half a year | DLB |
| 10  | Narcolepsy for 29 years and paroxysmal falls for 1 year | Narcolepsy |
| 11  | Numbness of two feet for 1 month, weakness of both lower limbs for 25 days | POEMS |
| 12  | Fever for 5 days, clouding of consciousness for 3 days | 1Epstein-Barr viral encephalitis 2MM |

MM: Multiple myeloma, POEMS: POEMS syndrome, MGAPU: monoclonal gammopathy-associated peripheral neuropathy, MGUS: monoclonal gammopathy of undetermined significance, ALS: Amyotrophic lateral sclerosis DLB: Dementia with Lewy body, IMD: Inflammatory mediated demyelination

**Discussion**

In clinical practice, OCB are often investigated in the diagnostic work-up of inflammatory CNS disorders, in particular MS and especially in the earlier stage of MS according to the McDonald criteria [12, 22]. Therefore, IgG isoelectric focusing followed by immunofixation electrophoresis is increasingly employed to be a routine laboratory technique for those patients with neuropathy to perform oligoclonal band analysis in order mainly to aid early differential diagnosis of multiple sclerosis. The mirror patterns are usually an incidental finding during CSF OCB analysis [23]. Due to the rarity, the laboratory interpretation to the mirror patterns is still often ambiguous [13], not to mention most neurologists involuntarily weaken the clinical significance of this patterns [4]. In this retrospective study, we spent more than four years focusing on the value of OCB analysis in the neurological diseases, ultimately only 12 cases which presented mirror patterns were screened out from 5892 patients. The very low detection rate of just only 0.2% indeed made the possible clinical implications overlooked. Subsequently, the 12 specimens were thoroughly analyzed combined with various clinical information.

First of all, 12 cases covered all types of the mirror patterns, among which only patient No.5 displayed
the pattern 3, patient No.6 and 11 were pattern 4, the remaining were pattern 5. For any equivocal bands, immunofixation is the definitive method to evaluate. The immunofixation electrophoresis demonstrated that three types of mirror patterns tightly linked with M protein. In our study, both the two pattern 4 cases (patient No.6 and 11) are positive for M protein; 7 out of 9 cases with mirror pattern 5 were related to M protein; well, only one patient with pattern 3 (patient No.5) are negative in M protein. Our findings, beyond the previous recognition that the pattern 4 mainly resulted from the systemic inflammation and pattern 5 implied the monoclonal gammopathy [8] suggested that 3 types of mirror patterns are all closely associated with M protein. Our considerations are based on that only one case of type 3 mirror pattern cannot preclude the possibility of M protein positive, case report by Chen had revealed that the same pattern 3 coexisted with IgG-κ monoclonal protein[10]. In addition, the significantly elevated intrathecal synthesis of 5 cases (No. 1,3,5,11,12) is in accordance with the QALB, which means more active immune reactions originate from perivascular infiltrates of B-lymphocytes through damaged blood-brain barrier. Consequently, the OCB results of 5 cases indeed presented relatively more prominent bands than other cases. Nevertheless, whether it’s prominent or subtle bands has nothing to do with M protein, which means the prominent bands doesn’t necessarily indicate the positive M protein and the subtle bands should also be alert to the presence of M protein. Our results demonstrated that mirror pattern bands primarily originated from peripheral serum M protein and also highlighted the valuable clinical implications of all the three types of mirror patterns.

Secondly, all the 12 cases started with neurological symptoms and subsequently admitted to the neurology department. But, eventually none of the 12 patients were diagnosed with MS. 8 out of 12 cases (patient No.1,2,3,4,5,7,8,11) were at the onset of atypical demyelinating lesion of peripheral nervous system. 6 out of 8 cases (patient No.1,2,3,7,8,11) are positive with M protein. All the above 6 patients except the patient No.7 were ultimately diagnosed with blood system disease after admission to the hospital, who benefited from timely detection of OCB and reasonable analysis without any delay. Moreover, the patient No.7 was confirmed with MM three years at follow-up after discharged from hospital. It makes sense that there exists a likely causal relationship between the
protein and peripheral neuropathy. The pathogenesis is thought to be a direct effect of M proteins on the peripheral nerve, resulting in a demyelinating process, which causes a series of clinical symptoms. Whereas, clinically, it’s very hard to distinguish monoclonal gammopathy-associated peripheral neuropathy from other cases of neuropathy due to the complexity of pathogeny. It’s of vital importance to the correct differential diagnosis, for the early treatment considerably improves patient outcome. Besides, it’s noteworthy that there were three patients (No.4,5,9) presenting mirror patterns with negative M protein. The three patients were respectively diagnosed with Amyotrophic lateral sclerosis, Inflammatory mediated demyelination and Dementia with Lewy body. However, unfortunately, so far it is still poorly understood why the mirror patterns appeared in the above three diseases.

Among the 12 patients included in our study, two cases (No.2 and 11) were diagnosed POEMS syndrome, three (No.3,7 and 8) were monoclonal gammopathy of undermined significance (MGUS) and two cases (No.1 and 12) were multiple myeloma (MM). The 58.3% positive rate of diagnosis of blood system-related disease was established on the premise that we didn’t rule out the possibility that patients with mirror patterns who didn’t diagnosed with blood system disorder in the short time were more likely to be diagnosed later. The presence of mirror patterns is though almost excluded the possibility of MS, provide an additional and powerful evidence to the diagnosis of blood system diseases. Amounts of researches show that MGUS is present in more than 3% to 4% of population older than age 50 years[24] and is regarded as a premalignant precursor of MM and often categorized as low-tumor-burden diseases as well [25] ADDIN EN.CITE , almost all cases of the MM are preceded by MGUS [26, 27] ADDIN EN.CITE . Based on the researches, it’s very necessary to close follow up for those patients (such as the No.6 and 10 in our study) with mirror pattern bands and positive M protein but not diagnosed as blood system disorder in the short term. In the following study, we still need to shed light on whether all the positive M protein can lead to the occurrence of mirror patterns no matter what types of or it just happens on the patients with neurologic disability. In addition, we also need next to figure it out what does it means that mirror patterns accompanied by negative M protein.
Conclusions

In summary, in this study, we firstly highlight the clinical significance of mirror patterns during cerebrospinal fluid oligoclonal band analysis, which absolutely cannot be underestimated, although out results are to certain degree limited by the relatively small sample size. Furthermore, we figure it out that all three mirror pattern bands closely connected with M protein. The analysis of OCB is very helpful for differential diagnoses. Any abnormal OCB bands could convey valuable diagnostic implications. It’s necessary for the patients with results of mirror pattern bands to perform immunofixation electrophoresis timely.

Method

1. Patients and Routine blood and CSF analysis

5892 patients with various neurological symptoms in the department of neurology in our hospital received CSF OCB analysis, of which the results of only just 12 patients displayed mirror pattern. Lumbar puncture and all specimens (CSF and serum) of these 12 patients were obtained for routine determination of IgG and albumin quantitation both in CSF and serum, evidence of intrathecal immunoglobulin synthesis (IgG-Syn) was based on the calculation according to the method of Reiber-Felgenhauer[18]. IgG-Syn demonstrates an immunologic reaction in the CNS, the upper limit of reference>9 is thought to have immune response[19]. CSF/serum albumin quotients (QALB=CSF albumin/serum albumin) is to assess the integrity of blood-CSF barrier. The upper reference limit of QALB×103>8 for the patients over 40 years predicts blood-CSF barrier disfunction[20]. In addition to laboratory parameters, we also analyzed the 12 patients in great detail with clinical characteristics including first clinical manifestations and suspected or confirmed diagnosis.

2. Oligoclonal band determination

IgG and albumin in CSF and serum were quantified respectively by kinetic nephelometry (Beckman Coulter IMMAGE800). Paired serum/CSF samples were used to analyze the IgG-specific OCB performed with IgG-isoelectric focusing on agarose gel followed by immunofixation (HYDRASYS FOCUSING, Sebia, France)[21]. Before IEF, serum samples were diluted in deionized water to reach the same IgG concentration as that of parallel CSF samples. Serum samples are run in parallel to CSF samples. The
patterns were interpreted qualitatively by comparing the presence or absence of OCB in CSF and serum. The present of two or more bands in the electrophoresis lanes are considered to be positive reaction[12].

Abbreviations
NO.: patient number, Age: patient age in years, CSF: cerebrospinal fluid, TP: total protein, OCB: oligoclonal bands, QALB: CSF/serum albumin quotient, IgG-Syn: intrathecal IgG synthesis, C-IgG: CSF IgG, S-IgG: Serum IgG, MS: multiple sclerosis, SIE: serum immunofixation electrophoresis, P3: pattern 3, P4: pattern 4, P5: pattern 5, ND: not detected; MGUS: monoclonal gammopathy of undermined significance; MM: Multiple myeloma, POEMS: POEMS syndrome, MGAPU: monoclonal gammopathy-associated peripheral neuropathy; ALS: Amyotrophic lateral sclerosis DLB: Dementia with Lewy body, IMD: Inflammatory mediated demyelination.

Declarations
Ethics approval and consent to the participate
This study was approved by the Ethics Committee of Xuanwu Hospital of Capital Medical University (Beijing, China), and written informed consent were obtained from all participants.

Consent for publication
All the authors have read and approved the paper for publication.

Availability of data and materials
All data generated or analyzed this study are included in the article.

Competing interests
The authors declare no conflicts of interest.

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Author’s contributions
Jinling Wang designed the study, collected and analyzed the data, and then wrote the manuscript.
Peichang Wang made the critical revision of the manuscript. All authors have given final approval of the version to the published.

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Figures
Figure 1

Results of isoelectric focusing electrophoresis and immunofixation electrophoresis in 12 cases with mirror patterns. (A) Isoelectric focusing of the patient’s CSF and Serum samples. C lane: CSF sample. S lane: corresponding serum sample. (B) Results of serum immunofixation electrophoresis in the corresponding patient.