中文題目：成人以週期性發燒為臨床表現之修格蘭氏症候群：病例報告及文獻探討

英文題目：Adult periodic fever as the manifestation of primary Sjogren's syndrome: A case report and literature review

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Introduction:

Periodic fever is characterized by cyclic fever and afebrile period with predictable duration. It can be caused by recurrent infection, malignancy, or noninfectious inflammatory disorders. Hereditary periodic fever syndromes are a group of disorders characterized by primary dysfunction of the innate immune system and usually manifest in children, however, only a limited number of patients experience disease onset during adulthood. It can be challenging to diagnose adults with periodic fever for years.

Periodic fever manifested in cases with autoimmune disease is rare when an associated viral/bacterial infection or malignancy is absent. Here, we reported a primary Sjogren's syndrome (pSS) case presenting with periodic fever, auditory hallucination and hearing impairment. We reviewed the literatures on fever and neurological symptoms in Sjogren's syndrome.

Case report :

A 56-year-old Taiwanese male suffered from periodic fever with a cycle of 6 days (fever > 39℃ for 3 days, then being afebrile for 3 days) for 5 years. The cyclic fever might disappear two months each year, but recurred. Besides fever, no systemic symptom occurred in the initial two years of fever. However, progressively impaired hearing developed since the third year of fever. Then auditory hallucination with repeated melody appeared. His fever once responded to nonsteroidal anti-inflammatory drugs for 3 months, but fever attacked again after discontinuing the drug. The laboratory data revealed no leukocytosis (WBC: 6400/μl, neutrophil: 71.4%, lymphocyte: 19.7%, eosinophil: 3.6%, monocyte: 4.8%). Laboratory assays revealed the levels of inflammatory markers, tumor markers, and cortisol in serum were all within the normal limits. Among the checked autoimmune markers (C3, C4, rheumatoid factor, antinuclear antibody, anti-neutrophil cytoplasmic antibodies, anti-ds DNA, anti-Sm, anti-SSA/Ro, anti-SSB/La, anti SCL-70, anti Jo-1, and

anti-RNP antibodies), and immunoglobulin G, A, and M, only mild decreased C3 level (75.6 mg/dl) and positive result for anti-SSA/Ro (10.6 IU/ml) were observed.

The pure tone audiometry of hearing ability revealed bilateral mixed type hearing impairment. No optic nerve atrophy or pale disc was found in ophthalmoscopy. No psychiatric disease was found with psychiatrist consultation. Computed tomography for brain, chest, and abdominal did not reveal any inflammatory process. The electroencephalogram showed normal cortical function. Ga-67 citrate whole body scan revealed no hot spots. The Schirmer's test showed positive result (right/left: 3mm/0mm in 5 minutes) and the Tc99m O4- salivary scintigraphy showed asymmetrical reduction of radiotracer uptake in left gland; chronic sialadenitis was suspected. Pathology of lip biopsy revealed lobules of mucoserous gland with aggregation of lymphocytes infiltrate, more than 50 lymphocytes / visual filed (400X). The lymphocytes were positive for leukocyte common antigen. PCR-sequencing of MEFV gene revealed no putative mutations for familial Mediterranean fever. A diagnosis of pSS was confirmed following the positive findings including hyposalivation, positive salivary scintigraphy, positive Schirmer's test, positive anti-SSA/Ro, and histopathological signs (focus score$\geqq$1) according to a revised version of the European criteria proposed by the American-European Consensus Group. With diclofenac 25 mg 4 times per day and prednisolone 20 mg per day, his fever subsided. Xerostomia and xerophthalmia improved at the same time. However, the auditory hallucination only partially improved. Prednisolone was tapered four months later and he remained afebrile for 10 months with diclofenac 25 mg 3 times per day.

Discussion :

Fever is present in 6 to 41% pSS cases. However, no detail of fever pattern of pSS was described in case series from 1997 to 2010 (Table 1). There is no case report of pSS presenting with periodic fever in literature. However, a few cases with autoimmune diseases had periodic fever and a possible correlation of autoimmunity and autoinflammation was postulated. Hereditary periodic fever syndromes (HPFSs) are genetic disorders that cause autoinflammation with main manifestations of cyclic fever and various inflammatory symptoms such as arthritis, serositis, conjunctivitis, and skin rash. HPFSs are usually present in the pediatric population with very few patients onset during adulthood. Our reported case is an Asian people with onset in adulthood and no putative gene mutation for familial Mediterranean fever was found.

He did not have HPFS symptoms and his laboratory data revealed no inflammation. The pSS case developed periodic fever before his pSS was diagnosed, and his fever, xerostomia and xerophthalmia responded to treatment of pSS. Though we observed periodic fever presented in a pSS case, the mechanism of the rare manifestation is unclear.

The occurrence of fever is significantly more common in pSS cases with neurological involvement than in those without neurological involvement. Interestingly, the burden of CNS involvement remains a debated issue with a high diversity in frequencies (Table 1) and variable manifestations. The incidence of mild to moderate psychiatric and cognitive impairment may be as high as 80% in patients with CNS-SS includding atypical mood disorder, psychosis, dementia, and histrionic personality presentation. Visual and auditory hallucinations as the clinical presentations were only reported in two cases respectively. Our patient's auditory hallucination with hearing impairment suggested neurological involvement of pSS.

In conclusion, we presented a rare but interesting case with periodic fever, auditory hallucination, hearing impairment in a pSS case. This report aimed to alert clinicians that fever and neurological manifestations were not uncommon in pSS cases.

Table 1 Summary of fever and neurological involvement from case series of pSS.

country	Case number	Fever %	Neuropsychiatric symptoms %	References
China	524	41%	11.9%	Lin et al, 2010
Italy	424	ND	5.8%	Massara et al, 2010
Spain	336	ND	7.1%	Ramos-Casals et al, 2005
Colombia	95	ND	3.2%	Anaya et al, 2002
Spanish	400	6%	8.3%	García-Carrasco et al, 2002
France	25	ND	39%	Lafitte et al, 2001
Greek	261	17	2.3%	Skopoulí et al, 2000
British	74	ND	5.4%	Davidson et al, 1999
China	116	15.6%	12.1%	Zhao et al, 1997
Japan	21	ND	14%	Tajima et al, 1997

ND: no data.