Original Article

IL-6 and IFNγ are elevated in severe mumps cases: a study of 960 mumps patients in China

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Abstract

Introduction**:** Mumps is a common infectious disease. Epidemics of mumps are reported globally every year and represent a threat to public health, especially in China and other developing countries.

Methodology: Clinical and laboratory findings of 960 mumps patients admitted to Beijing You'an Hospital, China, between January 2010 and December 2012 were collected and analyzed. Patients with isolated complication were selected and grouped as aseptic meningitis/encephalitis (AME) patients (n = 156) and Orchitis patients (n = 72). One hundred and fifty patients without complication were grouped as control. Levels of T cell subtypes and 8 serum cytokines were also tested.

Results: Majority of mumps patients were male (76.3%) and younger than 17 years old (76.2%). AME was complicated in 41.6% of mumps cases, and orchitis was in 21.3% (64.7% were left-sided). Unvaccinated patients had more chance to have AME or orchitis ($p = 0.034$ and 0.027). The rates of AME and orchitis in mumps patients rapidly increased during the last three years. No laboratory findings were associated with AME or orchitis (all $p > 0.05$). Serum IL-10 level was elevated in almost all patients. IL-6 and IFNγ levels were correlated with AME ($p = 0.025$ and $p = 0.018$). Their levels peaked at day one after admission, and started to decline thereafter.

Conclusions: This study suggests that the incidence of serious complications has become more common in recent years, moreover IL-6 and IFNγ may possibly be used as early serum markers for identifying patients with risk of developing complications in mumps.

Key words: Mumps, clinical features, cytokines, T cell subtypes

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Introduction

Mumps virus is an infectious pathogen common in humans, causing aseptic meningitis, encephalitis, orchitis or pancreatitis [1]. Although generally considered a mild disease in children, it may also have serious complications and detrimental sequalae, especially in adult patients, such as deafness or testicular atrophy [2]. Death can also be seen occasionally in severe cases [3].

The vaccine against mumps was developed in 1967 and applied worldwide, which led to a sharp decline of mumps incidence rate within a few years [4]. In China, the MMR (Measles-Mumps-Rubella) vaccine was included into the National Immunization Program since 1990's.

Despite good vaccination coverage in the world, major outbreaks have occurred in many countries, including developed countries, such as the United States, England, Canada, Belarus, Ireland, and others [4-15]. In China, since the application of the MMR vaccine, the incidence of mumps dropped remarkably, but recent national surveillance programmes still reported over 900,000 cases between January 2008 and December 2010, with a yearly incident rate of 22.8/100,000 in average [16]. The persistent occurrences of mumps cases have brought the global attention on the efficacy of vaccines and dynamic changes of the disease epidemiology. Careful evaluation is required to adopt effective public health measures.

The clinical diagnosis is not difficult in population with poor vaccine coverage. However, in most parts of the world, including China, due to the vaccine coverage present, clinical diagnosis of mumps can be complicated. It is always a question on how to make an accurate and early diagnosis in order to avoid

development of serious complications. Some aspects of the immune responses to mumps viral infection may be used in diagnosis, such as T cell subtypes in cellular immunity and different cytokine levels. Cytokines are key mediators in inflammatory processes during viral infections. Their levels have been found to be elevated in cerebrospinal fluid (CSF) of mumps patients complicated with aseptic meningitis [17]. Mumps virus is known to be able to suppress the Signal Transducer and Activator of Transcription (STATs), such as STAT1 and STAT3 [18-22], which are key mediators of gene expression and cytokine response to viral infections [23]. Genetic analysis also demonstrated that single nucleotide polymorphism (SNP) of certain cytokines and corresponding receptors may play a role in mumps pathogenesis [24,25].

The objective of this study was to summarize the clinical and laboratory data of a group of mumps patients admitted to Beijing You'an Hospital and evaluate the possible correlation that may exist between serum markers and disease severity, and complication onset. This study aims to characterize the current clinical features and epidemiology of mumps infections, and its dynamic changes in China. In addition, we intended to identify potential early serum marker(s) of disease severity, so that prophylactic measures can be taken to reduce the incidence of serious complications.

Methodology

Case definition

Mumps viral infection was defined as either the isolation of the virus from at least one site (throat, blood, stools, cerebrospinal fluid (CSF), or other), or a four-fold rise in mumps IgG antibody titer in acute and convalescent sera, with a negative bacterial culture. Aseptic Meningitis and/or Encephalitis (AME) was defined as a disease characterized by CSF pleocytosis, headache, neck stiffness, vomiting, lethargy and positive meningeal irritation signs in various combinations, with or without neuroimaging. Orchitis was defined as unilateral or bilateral testicular swelling and tenderness.

Study population

The study population consisted of 960 children who met the case definition described above. The patients were consecutively admitted to Beijing You'an Hospital, Capital Medical University (Beijing, P.R. China) between January, 2010 and December, 2012. After initial analysis, patients were selected and grouped into three categories based on disease severity: (1) Mild: mumps patients without AME or Orchitis; (2) AME: Mumps patients complicated with AME only; (3) Orchitis: Mumps patients complicated with orchitis only.

Data source

All parameters, except with kinetic level changes of IL-6 and IFNγ, included into the investigation, were collected by reviewing the patients' medical records archived into the medical record library and into the medical computerized database at Beijing You'an Hospital, Capital Medical University. The patients' records were retrospectively examined for the primary set of data, which included demographic characteristics (age and sex), clinical parameters (signs and symptoms), laboratory values (hematologic, biochemical and microbiological findings), radiologic data, patient's status at discharge (recovered or died), admission and discharge dates, and length of hospital stay (LOS). For kinetic level changes of IL-6 and IFNγ, nine typical patients (three from each of Mild, AME and Orchitis groups) were selected.

The Beijing You'an Hospital Ethics Committee has approved this study. It covered the retrospective analysis of the 960 records and the additional study of cytokine levels in nine patients. Parents or caretakers of all 960 participants and additional nine patients for cytokine research have given a written informed consent on behalf of their participating children for their information to be stored and used for research. Human experimentation guidelines of People Republic of China were followed in conducting this clinical research.

Cytokine level determination

Blood samples from all patients were collected at the time of admission for cytokine determination and cytokine levels were tested by two trained technicians immediately. Among 960 selected cases, nine typical patients were selected and blood samples were collected at day 0, day 1, day 2, day 3, and day 4 after admission. The plasma was harvested within 30 minutes of venipuncture at 37^{o}C from EDTA-anticoagulated blood samples and stored at -70^{o}C until analysis. The Bio-Plex Human 8-plex kit (Bio-Rad, Berkeley, USA) was used to detect IL-2, IL-4, IL-6, IL-8, IL-10, IFNγ, GM-CSF and TNFα levels on Luminex200 xMAP analyzer system (Luminex, Austin, USA), according to the manufacturer's instructions.

Statistical analysis

Proportional data were tested using χ^2 or Fisher's exact test. Continuous data were tested by Student's t-test. The Mann-Whitney U test was used for non-parametric data which did not have a normal distribution. All analyses were performed by SPSS software (version 11.0, SPSS). P value < 0.05 was considered to be significant.

Results

Patient characteristics and clinical and laboratory findings

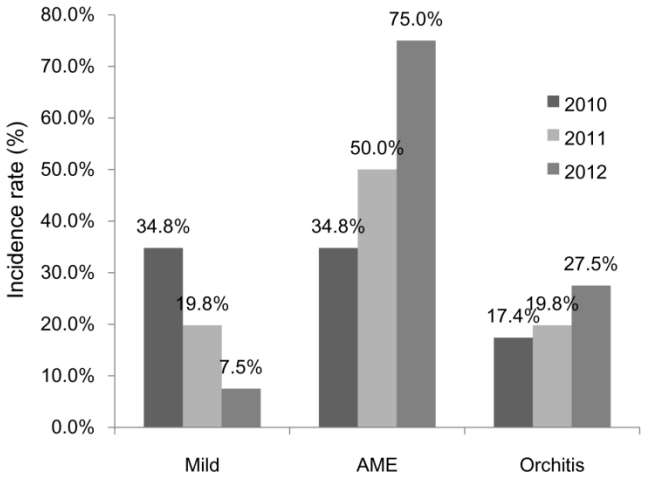
Data of totally 960 hospitalized patients with mumps admitted in Beijing You'an Hospital between January 2010 and December 2012 were collected. The average time from either fever or rash presented at hospital admission was 1.79±1.95 days. Hospital stay ranged from 2 to 25 days, with an average of 7.23±5.72 days. All patients in this study recovered and were discharged. No patient died. Patients who had received proper vaccination before the disease onset were 624 825/960 (6585.09%).

Among all 960 patients, 732 (76.3%) were male, and only 228 (23.7%) were female. The ratio of male over female is about 3:1. It appeared that males are more susceptible to mumps than females. However, the ratio did not show any significant difference among patients with different complications, thereby indicating that gender is not a risk factor for having complications. The average age of mumps patients was 12.42±9.58 years old. The patients' age ranged from one to 50 years old, where 23.8% were older than 17 years of age. From year 2010 to 2012, the ratio of patients older than 17 years of age fluctuated without significant change (2010, 21.4%; 2011, 27.1%; 2012, 18.9%).

Salivary gland swelling was the most common symptom, seen in 99.4% of the patients. Most of the swelling was bilateral (64.1%). Testicle pain was found in 21.3% of cases, most of which were left-sided (132/204, 64.7%). No paralysis was seen in any patient (Table 1). There was a significant number of patients having a fever higher than 39°C after admission, but no predictive value of fever on disease severity has been found (having complication or not, p > 0.05).

Among the 960 mumps patients, 150/960 (15.6%) were without any complications and defined as Mild. There were 399/960 (41.6%) cases complicated with AME, and 156/960 (16.3%) with orchitis. The rest, 255/960 (26.5%) patients were complicated with other disorders. Most of patients with AME were male (282/399, 70.1%), and only 29.3% (117/399) were female. Over the past three years, the incidence rates of complications in mumps patients have changed dynamically. Amongst mumps infected hospitalized patients, the rates of AME and orchitis both sharply peaked, as well as the incidence of AME even doubled in 2012 when compared to AME incidence in 2010 (Figure 1).

Figure.1 Incidence rates of AME and Orchitis in mumps. Mild: Mumps patients without any complications; AME: Mumps patients complicated with aseptic meningitis or encephalitis; Orchitis: Mumps patients complicated with orchitis



There were 825/960 (85.9%) patients who had received proper vaccination before the disease onset. By comparing patients with and without vaccination, we found that patients without vaccination had more chance to have severe complications such AME or orchitis (p = 0.034 and 0.027, respectively).

To further characterize patients with or without distinct complications, data from 150 mild cases, 156 with AME only, and 72 with orchitis only were collected and analyzed. Patients with multiple complications were excluded. Statistical data also demonstrated that total WBC, neutrophilic and lymphocytic count and other routine blood test results did not show any significant difference(s) among different groups of patients (p > 0.05) (Table 2).

T cell levels of mumps patients

The absolute count and percentage of lymphocytes in mild patients and patients with different complications did not differ significantly (Table 3). However, there may be some differences in immune-phenotypes. As shown in Table 3, CD3+, CD4+ and CD8+ cells count was subsequently analyzed.

Table 1 Clinical characteristics of mumps patients

	Case number (n)	Percentage (%)
Salivary gland swelling	954	99.4
Bilateral	615	64.1
Left-sided	192	20.0
Right-sided	138	14.4
Fever	888	92.5
Nausea	591	61.6
Headache	507	52.8
Vomiting	471	49.1
Abdominal pain	330	34.4
Testicle pain	204	21.3
Bilateral	30	3.1
Left-sided	132	13.8
Right-sided	42	4.4
Cough	177	18.4
Diarrhea	174	18.1
Enlarged lymph nodes	138	14.4
Chills	90	9.4
Drowsiness	66	6.9
Constipation	24	2.5

Table 2 Laboratory findings (Mean±SD (median))

	Mild (n = 150)	AME (n = 156)	Orchitis (n = 72)
WBC (10^9/L)	7.6±3.1 (6.6)	8.7±4.2 (5.4)	7.9±4.2 (6.2)
Neutrophils (%)	60.8±15.6 (61.5)	56.8±25.1 (59.5)	62.1±21.6 (67.5)
Lymphocytes (%)	32.2±14.4 (25.5)	45.8±35.2 (49.2)	39.2±25.6 (35.2)
HB (g/dL)	132.1±15.5 (132.0)	133.1±18.2 (130.2)	129.7±20.8 (133.2)
PLT (10^9/L)	255.7±82.2 (241.0)	265.2±98.5 (252.1)	251.1±84.7 (232.1)
CK (IU/L)	285.4±573.8 (71.0)	274.2±621.6 (129.5)	299.2±424.8 (207.3)
CK-MB (IU/L)	15.2±9.0 (14.0)	13.8±12.1 (12.9)	16.2±8.6 (14.6)
LDH (IU/L)	231.1±146.8 (213.0)	301.2±189.2 (288.2)	251.2±178.2 (233.3)
Serum amylase (IU/L)	605.1±532.1 (426.0)	743.4±459.3 (553.2)	592.3±394.3 (424.2)
Urine amylase (IU/L)	1987.3±2695.7 (1070.5)	2311.3±2523.8 (1502.3)	2130.9±2316.8 (1732.5)

AME: isolated aseptic meningitis/encephalitis

Table 3 CD4 T cells count in mumps patients (Mean±SD (median))

	Mild (n = 150)	AME (n = 156)	Orchitis (n = 72)
CD4+ T cells	981±553 (927)	1132±683 (1069)	1002±793 (993)
CD8+ T cells	421±254 (339)	593±530 (603)	467±197 (443)
CD3+ T cells	1309±459 (1279)	1637±787 (1534)	1498±831 (1374)

AME: isolated aseptic meningitis/encephalitis

Table 4 Plasma cytokine levels of mumps patients (Mean±SD (median))

Cytokine (pg/ml)	Mild (n=150)	AME (n = 156)	Orchitis (n = 72)
IL-2	3.4±1.8 (3.1)	5.7±3.8 (4.2)	4.4±2.9 (3.8)
IL-4	0.8±0.7 (0.7)	1.0±0.6 (1.1)	0.9±0.5 (0.9)
IL-6	18.1±11.6 (12.5)	25.2±17.6 (20.0)*	12.2±11.4 (27.5)
IL-8	29.4±21.9 (22.8)	31.8±32.8 (39.7)	28.8±34.4 (21.3)
IL-10	8.5±5.8 (9.4)	16.7±11.9 (15.6)	11.2±10.6 (12.2)
IFN□	74.1±53.1 (78.4)	128.7±79.8 (123.8)*	72.0±63.8 (74.1)
GM-CSF	8.4±7.7 (6.1)	9.5±6.2 (8.3)	8.6±8.9 (7.2)
TNF□	12.6±17.1 (15.2)	15.2±13.2 (18.0)	19.5±13.2 (18.0)

AME: isolated aseptic meningitis/encephalitis; *: $p < 0.05$;

The results of all these three cell types seemed elevated in patients with complications if compared to patients from the Mild group. Conversely statistical analysis failed to show any significant difference among groups (all $p > 0.05$).

Plasma cytokine levels of mumps patients

Cytokines are key mediators of different stages of immune responses to viral and bacterial invasion. The levels of IL-2, IL-4, IL-6, IL-8, IL-10, IFNγ, GM-CSF, and TNFα in all 960 patients were tested and described below. The levels of cytokines in three groups of selected subjects are presented in Table 4.

All tested cytokines were correlated to each other (all $p < 0.05$). It appears to be an activation of a well-connected cytokine network during Mumps viral infection.

For all 960 patients, the IL-10 levels were elevated in almost all patients (> 1.53ng/ml, 98.4%, 945/960). Levels of IL-6 and IFNγ were also above normal range (8.53pg/ml and 124.08pg/ml, respectively) in significant portion of tested patients (35.9%, 345/960 and 16.6%, 159/960, respectively). The elevation of IL-2, IL-4, IL-8, GM-CSF and TNFα levels were minimal.

Between Mild, AME and Orchitis groups, cytokine levels were further measured, compared and analyzed. The cytokine levels did not show significant changes between patients with different disease severity (all $p > 0.05$, AME, or Orchitis versus Mild group), except for IL-6 and IFNγ. Compared to patients in Mild group, the levels of IL-6 and IFNγ in patients from AME group were significantly elevated ($p = 0.025$ and $p = 0.018$, respectively). However, this difference was not observed between the Mild group and the Orchitis group ($p > 0.05$) (Table 4).

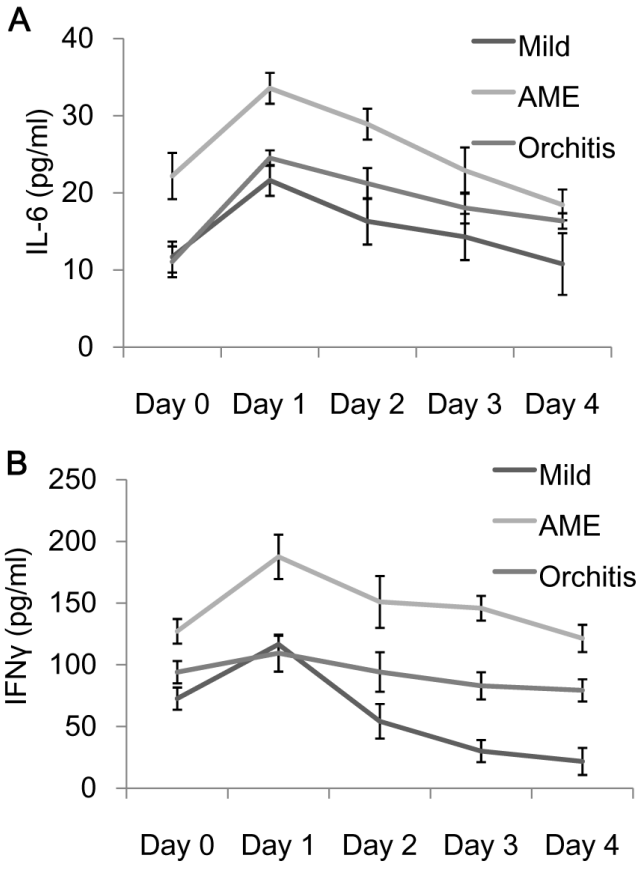
Kinetic changes of IL-6 and IFNγ in patients with severity differences

Mumps is a progressive disease and the cytokine levels change along with disease progression. We therefore monitored the kinetic changes in IL-6 and IFNγ levels within a small group of patients with or without different complication(s). In each type (Mild, AME, and Orchitis) of the Mumps patients, three typical patients were tested daily for IL-6 and IFNγ levels. Dynamic changes of IL-6 and IFNγ levels are shown in Figure 2. In all three groups, the IL-6 and IFNγ levels peaked at day one after admission and started to decline thereafter. The cytokine levels in mumps virus infected patients with AME were constantly higher than those in the other two types of patients. These results confirm that IL-6 and IFNγ levels are associated with the severity of mumps and also with the disease progression.

Discussion

Mumps is an important epidemic disease in China [16]. Following the wide use of the vaccine in recent years, the epidemic features of mumps have changed a lot. This study indicates that between 2010 and 2012, the percentage of mild cases dropped considerably, while the rate of severe cases with complications, especially AME, increased significantly (Figure 1). This indicates that the severity of mumps cases in China may be elevated. Although the death cases are still very rare, subsequent serious sequalae such as deafness as well as other neurological defects are

Figure.2 Kinetic changes of IL-6 and IFNγ in mumps patients with or without different complications. IL-6 (A) and IFNγ (B) levels were measured at day 0, 1, 2, 3, and 4 after admission. Mild: Mumps patients without any complications; AME: Mumps patients complicated with Aseptic Meningitis or Encephalitis; Orchitis: Mumps patients complicated with Orchitis.



alarming and they have to be taken into consideration with appropriate patient management.

Mumps can produce a spectrum of clinical manifestation. Based on results from this study, the salivary gland swelling (parotitis) was seen in almost all the patients, most of which was bilateral. Fever was also very common as the digestive tract is affected. It could also be caused by pancreatitis, gastroenteritis, or elevated intracranial pressure. Orchitis was observed more frequently on the left side for unknown reasons (Table1). All these findings were consistent with previous reports on mumps [1,2].

Cytokines are important mediators in many cellular signaling pathways involved in immune responses. IL-10 may have protective effects during inflammation by inhibition of IL-1, IL-6, IL-8, TNFα and reduction of reactive oxygen intermediates [26]. It can be activated in almost all inflammatory responses. In our study, IL-10 level was elevated in almost all mumps patients, but was not correlated with complication development $p > 0.05$). IL-6 is secreted by innate immune cells such as macrophages and dendritic cells. It could also be produced by non-leukocytes such as fibroblasts, endothelial cells, and astrocytes [27]. Elevated IL-6 concentration is associated with severe inflammatory diseases and malignancies [28]. IFNγ is a pleiotropic cytokine that is produced mainly by Th1 cells, cytotoxic CD8+ T cells and NK cells. It is critical for both innate and adaptive immunity, and could be activated by viral infections [29]. Our findings demonstrated that elevation of IL-6 and IFNγ levels measured after admission was related to AME, a severe complication in mumps patients (Table 4). Dynamic changes of these two cytokines also explain the possible association that may exist between IL-6 and IFNγ with disease severity and complications. In addition, it indicates that IL-6 and IFNγ peaked early at day 1 after admission (Figure 2). Xu *et al* recently reported that the V protein of mumps virus blocks IFNγ and IL-6 expression and signaling [30] together with previous publications [18-20], suggesting critical roles of IL-6 and IFNγ in mumps viral infection. These cytokines may be used as serum markers to make early diagnosis of AME in mumps and to take early measures during the course of the disease. Thus, additional prospective studies should be conducted to investigate the predictive value of these two cytokines in mumps. Further studies on a larger population of patients are also required to confirm this finding. With these confirmatory investigations, we would be more confident to use these cytokines as predictive markers to guide clinical practice.

In conclusions, our study suggests that the incidence of serious complications has become more common in recent years, and IL-6 and IFNγ may be used as early serum markers for patients that show the development of complications such as AME in mumps.

Acknowledgements

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