# An adult case of hand, foot, and mouth disease caused by enterovirus 71 accompanied by opsoclonus myoclonica

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**We reported a 23-year-old female who was treated for rash due to hand, foot, and mouth disease (HFMD). On day 4 of hospitalization, the patient showed opsoclonus (jerky eye movements in all directions), myoclonus of the neck, trunk, and extremities, and cerebellar ataxia. Based on the changes in serum viral antibody titer, the patient was diagnosed as enterovirus 71 infection. No obvious abnormal findings were noted in head MRI. Immunoglobulin 5 g/day was administered for 3 days in the early stages of infection, and administration of methylprednisolone 500 mg/day for 3 days was repeated twice. Afterwards, oral corticosteroids were given, resulting in neurological improvements a month. Including our case, there are only 2 cases within opsoclonus myoclonica associated with enterovirus 71 infection. Our case suggests, based on the course of treatment, possible involvement of direct viral action or autoimmune response in opsoclonus myoclonica.**

**Key words: opsoclonus myoclonus syndrome, enterovirus 71, adult patient**

## INTRODUCTION

Opsoclonus myoclonica is relatively rare resulting mainly from idiopathic causes, but is sometimes associated with paraneoplastic syndrome, post infectious encephalopathy, encephalitis, thalamic hemorrhage, drug intoxication, and brain tumor[1)]. HFMD is an acute viral infection prevalent mostly in infants and is caused primarily by coxsackie A16 and enterovirus 71, although several other kinds of virus have been identified. Reports of neurological manifestations in an adult with enterovirus 71 are rare. We encountered an adult case of HFMD due to enterovirus 71, who showed opsoclonus myoclonica.

## CASE

The case was a 23-year-old female who showed bullous eruptions on the distal portion of the extremities on June 2003. She was seen by Dermatology at another hospital and was diagnosed as HFMD. Afterwards, the patient had a fever of over 39.0℃, headaches, nausea, and vomiting, so she was admitted by Dermatology at this hospital. After admission, the patient manifested dizziness, gait disturbance, and abnormal eye movements, so she was transferred to Neurology for further evaluation and treatment. The patient's post history included acute pyelonephritis at age 7, acute suppurative tonsillitis at age 8, and infectious mononucleosis at age 15. There was nothing remarkable in the patient's family history.

## PHYSICAL FINDINGS

General physical findings were a temperature of 39.3℃, BP of 110/50 mmHg, and pulse rate of 60 beats/min. Heart sounds were normal without audible murmurs, breath sounds were also normal, there were no abnormal findings in the abdomen, and edema was also not noted. The cutaneous lesions were found the palms and soles, erythematous macules and grayish oval vesicles, 2 to 4 mm in size. Almost lesions run parallel to skin lines. Vesicles were atonic and tender (Fig. 1).

Neurological examinations revealed that the patient was alert and higher cerebral functions were normal. Pupils were 3.5 mm in size and reactive to light; opsoclonus (jerky eye movements in all directions) was evident, though restriction of eye movements was not noted. There were no abnormalities in other cranial nerves. Myoclonus of the neck, trunk, and extremities was noted, and the patient was unable to walk because of ataxia of the trunk and extremities. There were no motor or sensory abnormalities, deep tendon reflexes were normal, and pathological reflexes were negative.

## LABORATORY FINDINGS

Results of blood test were as follows: WBC 7900/$\mu$L, RBC 478×104/$\mu$L, Hb 14.4 g/dL, Ht 42.3 %, Plt 25.6 × $10^4$/$\mu$L, TP 7.4g/dL, AMY 63 IU/L, BUN 11 mg/dL, Cr 0.56 mg/dL, UA 4.3 ng/dL, Na 140 mEq/L, K 3.8 mEq/L, Cl 104 mEq/L, Ca 8.9 mg/dL, T-Bil 0.6 mg/dL , GOT 14 IU/L, GPT 13 IU/L, LDH 134 IU/L, $\gamma$-GPT 38 IU/L, ALP 190 IU/L, CPK 31 IU/L, CRP 0.51 mg/dL, and Glu 115 mg/dL. Thus, only a

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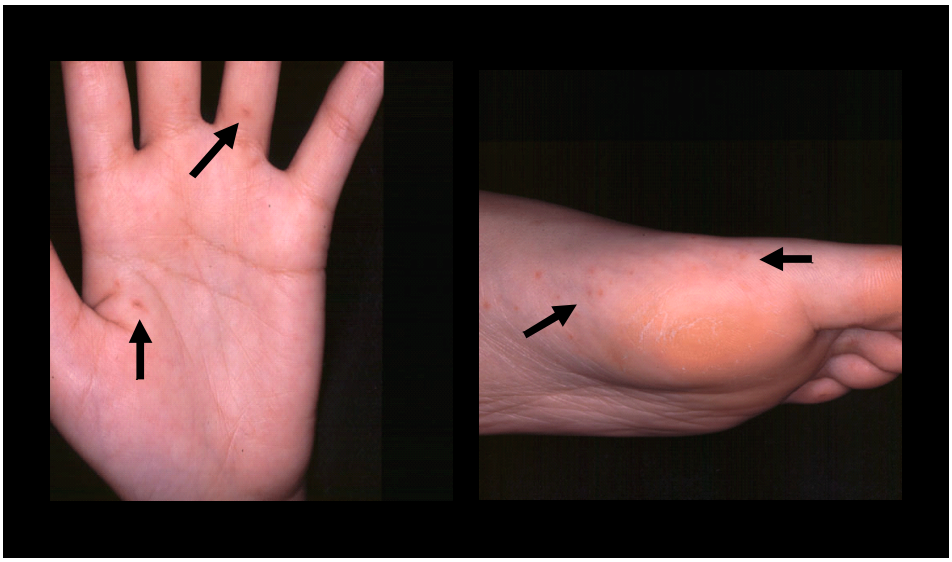

**Fig. 1.** Erythematous macules and atonic, grayish vesicles were noted on the palms and soles.

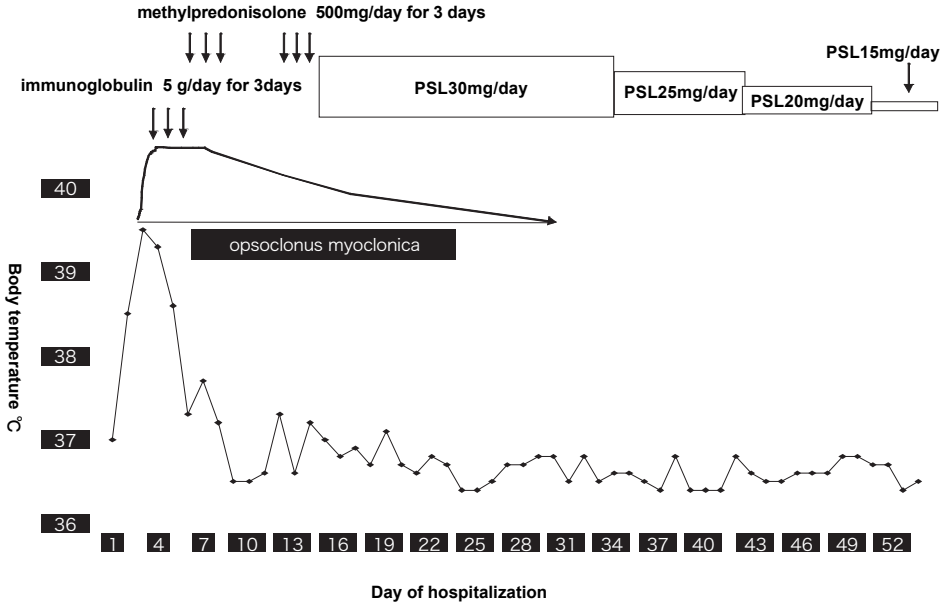


**Fig. 2.** On day 3 of hospitalization, opsoclonus myoclonica rapidly manifested. Intravenous administration of immunoglobulin and methylprednisolone and oral corticosteroids resulted in improvement over the course of about a month.

mild inflammatory response was noted. Serum viral antibody titers to enterovirus 71 were 1 : 64 (6/13), 1 : 128 (6/27), and 1 : 64 (7/18), and antibody titers to coxsackie B1, coxsackie B3, coxsackie A10, and coxsackie A16 were all less than 1 : 4. CSF findings were as follows: pH 8.2, specific gravity 1.106, cell count 21/ $\mu$l (1 mononuclear cell, 20 polymorphonuclear cells), glucose 70 mg/dL, protein 52mg/dL, and Cl 111 mEq/L; an elevated cell count and protein level were noted. A head MRI was performed twice in June and once in July, but abnormal findings were not found in any of the images.

## COURSE

The clinical course of the case is shown in Fig. 2. Treatment was as follows: on day 5 of hospitalization, intravenous immunoglobulin 5g/day was administered for 3 days; intravenous methylprednisolone 500mg/day was repeated twice from day 8 to day 10 and from day 14 to 16 of hospitalization. Afterwards, oral corticosteroids were given and then gradually reduced. Some improvements in neurological manifestations were noted after completion of the first cycle of methylprednisolone therapy, and the neurological manifestations disappeared completely on day 31 of hospitalization. With regard to eye movements, opsoclonus in all direc-

**Table** Cases of opsoclonus myoclonica associated with enterovirus 71 infection.

| Case | Age (y/o) | Sex | Clinical presentation | Rash | CSF | |
|---|---|---|---|---|---|---|
| | | | | | Protein | WBC count Cell/$\mu$l |
| McMinn et al (2001) | 1.6 | F | Opsoclonus myoclonica 3 weeks after the development of rash | HFMD | 0.13 g/dl (normal: 0.15-0.45) | 1 |
| Our case | 23 | F | Opsoclonus myoclonica 3 days after the development of rash | HFMD | 52 mg/dl (normal: <40) | 21 |

tions was noted on day 7, 3 days after immunoglobulin administration, but methylprednisolone 500mg/day has a therapeutic effect on opsoclonus.

## DISCUSSION

Clinical manifestations related to enterovirus 71 infection include aseptic meningitis, poliomyelitis-like paralysis, brainstem encephalitis, neurogenic pulmonary edema, cerebellar ataxia, Guillain-Barre syndrome, and transverse myelitis[2–4], but opsoclonus myoclonica is rare[3]. There are occasional reports of opsoclonus myoclonica associated with an enterovirus infection[5–7]. Only one case of opsoclonus myoclonica associated with enterovirus 71 infection was reported previously McMinn et al.[3]. The case was a childhood, but our case was adult onset.

The foci responsible for the onset of opsoclonus myoclonica have been associated with the brainstem and dentate nucleus of the cerebellum[3, 8]. MRI was unable to identify these foci, but damage to the same sites is thought to have caused opsoclonus myoclonica in the present case as well.

With regard to the mechanism of opsoclonus muoclonica, repeated MRI examinations in our case failed to show abnormal signals and severe neurological manifestations like impaired consciousness were also absent, suggesting little possibility of direct tissue damage by the viral infection itself. Citing Pranzatelli[9], Glatz et al. stated that "among various etiologies of opsoclonus-myoclonus syndrome, paraneoplastic, paraviral, or idiopathic encephalitis are the most common causes, and an autoimmune-mediated brain stem dysfunction is the suggested underlying pathomechanism"[10]. In addition, both patients responded well to corticosteroids, the opsoclonus myoclonica in enterovirus 71 infection is also suspected to be related to the autoimmune mechanisms. Nevertheless, the patient cited by McMinn et al. manifested opsoclonus myoclonica 3 weeks after the onset of a rash and had a normal CSF cell count at that point. In contrast, our patient showed it relatively early i.e. 3 days after the onset of a rash and an elevated CSF cell count (Table). These facts indicate that opsoclonus myoclonica related to enterovirus 71 infection may occur as a post-infectious or para-infectious mechanism. In our patients, immunoglobulin was administered relatively soon after the onset of a rash and subsequent therapy with corticosteroids resulted in rapid improvement of the manifestation.

## CONCLUSION

An adult case of hand, foot, and mouth disease due to enterovirus 71 with opsoclonus myoclonica was reported. Infection due to enterovirus 71 is known to be associated with severe neurological complications such as brainstem encephalitis, but opsoclonus myoclonica is rare. In the case, administration of immunoglobulin to treat a rash that developed in the early stages of infection and later administration of corticosteroids led to rapid improvement of opsoclonus myoclonica suggesting an autoimmune mechanism via a para-infection.

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