# Childhood acute flaccid myelitis, including the first confirmed cases of enterovirus D68 myelitis in Singapore and Southeast Asia

**Jillian Ann Pakiam[1], Karen Donceras Nadua[2], Lin Cui[3], Hoh Sing Yee[4], Tan Ling Ying[4], Chew Ee Ming[5], Andrew Kian Tuck Yam[5], Teo Jia Hui[4], Ng Zhi Min[4], Indra Ganesan[6], Chong Chia Yin[2], Terrence Thomas[4]**

[1]General Paediatric Service, [2]Infectious Disease Service, [4]Neurology Service, [6] Nephrology Service, Department of Paediatrics, [5]Department of Orthopaedic Surgery, KK Women's and Children's Hospital, Singapore, [3]National Public Health Laboratory, Singapore

## INTRODUCTION

Acute flaccid myelitis (AFM) has been reported in Southeast Asia usually in association with hand, foot and mouth disease (HFMD) due to Enterovirus A71, or rarely with vaccine-associated paralytic poliomyelitis.[1]

We report the epidemiology, treatment and outcomes of AFM in Singapore, including the first two cases of enterovirus D68 (EVD68) myelitis in Southeast Asia.

## METHODOLOGY

- A retrospective study from KK Women's and Children's Hospital, Singapore from from January 2012 to December 2022.
- Demographics, clinical, laboratory, neuroimaging and outcome data were analysed.
- Laboratory investigations included respiratory, stool and cerebrospinal fluid viral reverse transcription polymerase chain reaction (RT-PCR) for pathogens and relevant antibodies assays.
- At physician's discretion, patients positive for enterovirus were further genotyped for EVA71 and EVD68.
- Severity of spinal cord involvement was scored using the American Spinal Injury Association (ASIA) Impairment score at nadir, whilst the modified Rankin Scale (mRS) was used to classify disability at nadir and last follow up. We defined an mRS score of 2-3 as moderate disability and 4-5 as severe disability.

**Figure 1. Diagnostic algorithm for cases with suspected acute flaccid myelitis**

Clinical features
- Acute onset of weakness following an illness, usually febrile and respiratory
- Neurological findings of flaccid weakness and hyporeflexia, +/- cranial nerve or bladder/bowel involvement

↓

Neuroimaging
- MRI whole spine (prioritised) and MRI brain with T2 and T1 pre-contrast and post-contrast sequences in both axial and sagittal planes
- Grey-matter predominant T2 hyperintensity of the spinal cord, lesions are usually longitudinally extensive and non-enhancing

↓

Laboratory Evaluation

| | |
|---|---|
| **Respiratory samples** : | Respiratory viral panel RT-PCR testing (with pan- enterovirus RT-PCR) |
| Stool samples: | Enterovirus RT-PCR, viral culture for poliovirus* |
| CSF sample: | Cell counts, protein, glucose, oligoclonal bands<br>Enterovirus RT-PCR , other microbiological tests e.g. West Nile virus or Japanese Encephalitis serology/RT-PCR depending on epidemiology |
| Blood sample: | MOG IgG, aquaporin-4 IgG, GQ1b IgG to test for alternative myelopathies<br>Epidemiologically appropriate microbiological tests as above |

*2 stool specimens submitted within 14 days of symptom onset under the AFP surveillance program in Singapore

↓

Genotyping
- Positive enterovirus RT-PCR results to be serotyped for EVD68 and EVA71

## RESULTS

A total of 8 cases met inclusion criteria. The first patient (A1) was an isolated case in 2012 whilst the 7 others clustered over two periods from July 2018 to January 2019 and from April to August 2022

- Median age was 3 (IQR 2.2- 10.0) years, and all (100%) were male
- Presenting features were a preceding febrile respiratory illness (n=6) or hand-foot-and-mouth disease (n=2), upper limb weakness (n=5, 62.5%), and neurogenic bladder (3, 37.5%)
- Spinal cord lesions mainly involved the cervical region (7, 87.5%), all (100%) were predominantly grey matter
- 5 (62.5%) patients had elevated CSF white cells (median 7.5/mm$^3$ (IQR 2.8-40.3)) and 6 (75.0%) patients had elevated CSF protein (median 0.6g/L (IQR 0.4-0.7)). CSF was negative for pathogens.
- Two of 4 patients (50%) with enterovirus detected in respiratory/rectal swabs had genotype D68 (2022 cluster) **(Table 1)**

**Table 1. Enterovirus Genotyping for the 8 patients**

| Patient | Pan-Enterovirus RT-PCR | Sample site (Pan-EV+ or -) | EVD68 RT-PCR | EVA71 RT-PCR |
|---|---|---|---|---|
| A1 | Negative | stool (-); throat/nasal swab (np) | np | (-) |
| A2 | Negative | stool (-); throat/nasal swab (-) | np | np |
| A3 | Positive | stool (+); throat swab (-) | np | throat (-)<br>stool np |
| A4 | Negative | stool (-); throat swab (-) | (-) | (-) |
| A5 | Negative | stool (-); throat/nasal swab (-) | np | np |
| A6 | Positive | stool (-); throat swab (+) | np | stool (-)<br>throat np |
| A7 | Positive | stool (-); throat/nasal swab (+) | (+) | (-) |
| A8 | Positive | stool (+); nasal swab (+) | (+) | (-) |

**Footnote: All patients were negative for enterovirus in cerebrospinal fluid; + = positive result; - = negative result; np = not performed**

- All received intravenous methylprednisolone, 6 (75%) had additional intravenous immunoglobulin and either plasma exchange therapy (n=1) or intravenous tocilizumab (n=1)
- Median modified Rankin Scale (mRS) at acute illness was 4 (IQR grades 3-5), with an improvement (median 2 (IQR 1.8-2.3) mRS grades) on follow-up (median duration 3.7 (IQR 1.4-4.1) years)
- One patient (12.5%) had a full recovery and 7 (87.5%) have moderate disability (mRS 2-3). Predominant disability is motor function impairment; patient A5 has persistent urinary voiding dysfunction at 16$^{th}$ month review
- Patient A3 underwent nerve transfer surgery at 10- and 38-months post illness for right upper limb monoplegia, with improvement in function of upper limb

## DISCUSSION

- Clustering of EVD68-related AFM during EVD68 epidemics is well described in literature and demonstrated in our cohort, with clinical presentation like that seen in our patients [2]
- Despite aggressive immunotherapy, the disability risk is high in patients with AFM. Up to 90% of patients recover with significant disability as opposed to 40% with significant disability in children with idiopathic transverse myelitis (TM). [3] Only 1 (12.5%) patient in our series made a full recovery, 5 (67.5%) had residual deficits with 4 (50%) requiring orthotics walk independently.
- EVA71 is long associated with encephalomyelitis and AFM, but none in our cohort were positive for EVA71 even in 2 patients with HFMD
- EVD68 has previously not been detected in patients with AFM in Singapore or Southeast Asia, although data from Singapore, Thai and Malaysian studies have demonstrated that this strain has already been circulating in the region. [4]

- Underestimation of EVD68 prevalence in Singapore likely due to lack of an active surveillance program
- We provide an algorithm **(Figure 1)** for evaluation of patients with suspected AFM as early recognition of an outbreak is important so that education and interventions can be instituted promptly to reduce morbidity from AFM

## CONCLUSION

EVD68 was confirmed using respiratory and/or stool sampling in 2 of our 8 patients with AFM and should be considered in all children presenting with AFM in Southeast Asia. Despite treatment, AFM patients have a high risk of disability. Efforts should be made to detect and serotype enterovirus in patients with AFM.

## REFERENCES

1. Hussain IH, Ali S, Sinniah M, et al. Five-year surveillance of acute flaccid paralysis in Malaysia. J Paediatr Child Health 2004;40:127-30.
2. Messacar K, Schreiner TL, Van Haren K, et al. Acute flaccid myelitis: A clinical review of US cases 2012-2015. Ann Neurol 2016;80:326-38.
3. Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. Lancet 2021;397:334-46.
4. Linster M, Donato C, Mah MG, et al. Genetic diversity of respiratory enteroviruses and rhinoviruses in febrile adults, Singapore, 2007-2013. Influenza Other Respir Viruses 2020;14:67-71.