Case report: Novel treatment regimen for enterovirus encephalitis in SCID

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Most non-polio enterovirus infections in immunocompetent individuals are acute and self-limiting in nature; however, infection can be severe, chronic and have devastating outcomes in immunocompromised hosts. Therapeutic strategies have predominantly involved supportive care, with the lack of approved antiviral treatments proving challenging for management. We report a case of an 8-month-old child who presented with severe enterovirus encephalitis following gene therapy for X-linked severe combined immunodeficiency (X-SCID) and who demonstrated clinical and microbiological improvement after a novel regimen of favipiravir, fluoxetine, and high-dose intravenous immunoglobulin (IVIg). The patient presented 6 weeks post–gene therapy with rapid neurological deterioration in the context of incomplete immune reconstitution, with microbiological and radiological evidence confirming enterovirus encephalitis. His neurologic examination stabilised 8 weeks after treatment, and he subsequently demonstrated excellent immune recovery. This is the first case report of combined therapy with favipiravir, fluoxetine, and high-dose IVIg in the context of severe enterovirus encephalitis in an immunocompromised host. This case highlights the importance of considering enterovirus encephalitis in immunocompromised patients presenting with both acute and chronic neurological signs, as well as developmental regression. The demonstrated
**Introduction**

*Enteroviruses* are small RNA viruses from the picornaviridae family, a genus of 12 species of which seven infect humans, ranging from *Enterovirus* A, B, C, or D and Rhinovirus A, B, and C. While most non-polio *enterovirus* infections in immunocompetent individuals are self-limiting, infections in immunocompromised hosts can become chronic and severe.

There is a lack of approved antiviral treatments for *enterovirus* infections that presents a particular challenge in immunocompromised individuals. We report an 8-month-old child who presented with *enterovirus* encephalitis 6 weeks post-gene therapy for X-linked severe combined immunodeficiency (X-SCID), with clinical and microbiological improvement after a novel regimen of favipiravir, fluoxetine, and high-dose intravenous immunoglobulin (IVIg).

**Case report**

The child was born at term to non-consanguineous parents with an uneventful neonatal period. He developed recurrent bacterial infections from 1 month of life, with omphalitis and bilateral ear and prepucial discharge, positive for *Stenotrophomonas maltophilia* and *Streptococcus pyogenes*. He had an 8-week history of cough and was found to be Polymerase Chain Reaction (PCR) positive for rhinovirus on nasopharyngeal aspirate. His infectious history, in addition to a skin rash and eosinophilia suggesting possible Omenn syndrome, prompted investigation for primary immunodeficiency. There was no significant family history of recurrent infections or diagnosed inborn errors of immunity. His total lymphocyte count was normal (3.78 × 10⁹/L); however, he had marked T and NK cell lymphopaenia with 50/µl CD3+ T cells, 20/µl CD4+ T cells, and undetectable naive T cells. Lumbar puncture demonstrated a raised white cell count (WCC) of 23 × 10⁶/L, protein of 1.06 g/L, glucose of 2.3 mmol/L, and elevated Interleukin 6 level at 105 pg/ml. Cerebrospinal fluid (CSF) *Enterovirus* PCR was positive with a cT value of 35.18, subsequently identified by deep sequencing as Coxsackievirus B1. Blood PCR was negative for *enterovirus*; however, both stool and Nasopharyngeal aspirate (NPA) were positive with cT values of 34.9 and 27.4, respectively. Retrospective analysis of an NPA sample prior to gene therapy was equivocal for *enterovirus* with a cT value of 38.44.

MRI demonstrated abnormal T2 signal in thalami and brainstem with some restricted diffusion suggestive of viral encephalitis (Figure 2). He commenced treatment with IVIg 1 g/kg weekly, favipiravir, and fluoxetine after receiving approval from the hospital Drugs and Therapeutics Committee (DTC). Oral favipiravir was dosed initially at 500 mg/500 mg/200 mg 8 hourly on day 1, followed by 200 mg three times a day thereafter. Oral fluoxetine was initiated at a low dose of 2.5 mg daily and titrated to a maximum dose of 0.75 mg/kg/day. Treatment was associated with clinical improvement, with resolution of encephalopathy, improvement in limb dystonia, and no further paroxysmal eye movements.

At 6 months old, he underwent lentiviral gene therapy with low-dose busulfan conditioning. Prior to mobilisation and harvest of haematopoietic stem cells, he received a short course of oral steroids to treat an underlying inflammation, as suggested by eczematous skin rash, thrombophilia, and eosinophilia. This improved his symptoms. He was discharged 3 weeks following cell infusion.

At 6 weeks post–gene therapy, he developed rapid neurological deterioration with bilateral squint, inability to fix and follow, upgazing episodes, limb dyskinesia and dystonic movements, truncal hypotonia, and encephalopathy (Figure 1). His symptoms developed while on a prophylactic antimicrobial regimen of co-trimoxazole, phenoxymethylpenicillin, ciprofloxacin, acyclovir, immunoglobulin replacement, and itraconazole. He had no fevers or other infective symptoms, rashes, feeding issues, or gut symptoms. Cardiovascular, respiratory, and abdominal examinations were unremarkable, and there was no lymphadenopathy. Immune recovery was emerging with 40/µl CD3+ T cells, 20/µl CD4+ T cells, and undetectable naive T cells. Lumbar puncture demonstrated a raised white cell count (WCC) of 23 × 10⁶/L, protein of 1.06 g/L, glucose of 2.3 mmol/L, and elevated Interleukin 6 level at 105 pg/ml. Cerebrospinal fluid (CSF) *Enterovirus* PCR was positive with a cT value of 35.18, subsequently identified by deep sequencing as Coxsackievirus B1. Blood PCR was negative for *enterovirus*; however, both stool and Nasopharyngeal aspirate (NPA) were positive with cT values of 34.9 and 27.4, respectively. Retrospective analysis of an NPA sample prior to gene therapy was equivocal for *enterovirus* with a cT value of 38.44.

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**Keywords**

case report, primary immunodeficiency diseases, *enterovirus*, infectious encephalitis, antiviral agents, severe combined immunodeficiency, gene therapy (GT)
His neurological progress plateaued 4 weeks after initiation of therapy, with intermittent dystonia and an evolving hypertonia. His developmental regression was ongoing, having not yet regained independent sitting, no longer reaching purposefully for objects, or vocalising or smiling as previously. However, he was felt to have an overall improvement in his neurologic examination since the beginning of his admission, particularly his eye movement disorder, and he was demonstrating better head control. IVIg frequency was reduced from weekly to monthly, as previously planned, and gabapentin and clonidine commenced for limb hypertonia. A repeat CSF at this point demonstrated an equivocal result for enterovirus PCR with a cT of 38.22, a WCC of $24 \times 10^6/L$, protein of $0.75 g/L$, and glucose of $2.4 \text{ mmol/L}$. At 6 weeks after therapy initiation, the CSF was negative for enterovirus, with a reducing WCC of $10 \times 10^6/L$ and protein of $0.57 g/L$.

He experienced significant ongoing dyskinesias despite decreasing and ultimately negative enterovirus loads in the CSF and repeat MRI not suggestive of ongoing inflammation. It was hypothesised that he was developing an emerging
| Months post-Investigational Medicinal Product (IMP) | Pre-Investigational Medicinal Product (IMP) | 0–1 | 1–2 | 2–3 | 3–4 | 6 | Units |
|-------------------------------------------------|---------------------------------------------|------|-----|-----|-----|---|-------|
| **Immunology**                                  |                                             |      |     |     |     |   |       |
| Lymphocyte count                                |                                             | 3,780| 3,120| 4,510| 6,550| 4,070| cells/µl |
| CD3+ T Cells                                    |                                             | 50   | 40  | 40  | 800 | 2,840| cells/µl |
| CD19+ B Cells                                   |                                             | 3,660| 2,100| 4,090| 5,470| 1,030| cells/µl |
| CD16+56+ NK Cells                               |                                             | 20   | 820 | 290 | 160 | 90  | cells/µl |
| CD3+CD4+ T cells                                |                                             | 40   | 10  | 20  | 630 | 1,410| cells/µl |
| CD3+CD8+ T cells                                |                                             | 10   | 0   | 0   | 70  | 390 | cells/µl |
| Naive CD4+ T cells                              | Undet                                      | Undet| Undet| Undet| 630 | 2,410| cells/µl |
| Naive CD8+ T cells                              | Undet                                      | Undet| Undet| Undet| 70  | 390  | cells/µl |
| PHA Stimulation                                 |                                             |      |     |     |     |     |       |
| Common gamma chain (γc) expression              | Equivalent to control                      |      |     |     |     |     |       |
| Signal transducer and activator of transcription 5 (STAT5) Phosphorylation | Absent in response to Interleukin 2 (IL-2); Interleukin 7 (IL-7); Interleukin 15 (IL-15) |      |     |     |     |     |       |
| Maternal engraftment                            | Nil                                         |      |     |     |     |     |       |
| **Microbiology**                                |                                             |      |     |     |     |     |       |
| Epstein-Barr Virus, CMV = Cytomegalovirus (EBV), Cytomegalovirus (CMV), Adenovirus PCR (Blood) | Negative | Negative | Negative | Negative |       |       |
| Respiratory Viral Panel PCR                     | Rhinovirus                                  |      |     |     |     |     |       |
| Diagcore Respiratory Panel PCR                  | Rhinovirus/enterovirus: cycle threshold (cT) 22.0 |      |     |     |     |     |       |
| Stool Microbiology (Culture & PCR)              | Negative                                   | Negative | Negative | Negative |       |       |
| CSF Microbiology (Culture & PCR)                | Negative                                   |       |       |       |       |       |
| **EnteroVirus PCR**                             |                                             |      |     |     |     |     |       |
| NPA                                             | Equivocal: cycle threshold (cT) 38.44       |      |     |     |     |     |       |
| CSF                                             | cycle threshold (cT) 27.42                  |      |     |     |     |     |       |
| Blood                                           | Negative                                   | cycle threshold (cT) 35.18                 |     |     |     |     |     |
| Stool                                           | Negative                                   | cycle threshold (cT) 34.93                 |     |     |     |     |     |
| **CSF-Other Parameters**                        |                                             |      |     |     |     |     |       |
| CSF White Blood Cell (WBC)                      | 23                                         | 24   | 10  | 6   | × 10^9 | L |
| CSF Red Blood Cell (RBC)                        | 4                                          | <1   | <1  | <1  | × 10^6 | L |
| CSF Glucose                                     | 2.3                                       | 2.4  | 2.7 | mmol/L |     |     |
| CSF Lactate                                     | 1.6                                       | 1.5  | mmol/L |     |     |
| CSF Protein                                     | 1.06                                      | 0.75 | 0.57 | 0.3 | g/L   |     |
| CSF IL 6                                        | 105                                       | 47.81| 25  |     | pg/ml |     |

* = Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, Coronavirus HKU1, Rhinovirus, Enterovirus.

* = Influenza A, Influenza B, Influenza A H1N1, Coronavirus 229E, Coronavirus OC43, Coronavirus NL63, Coronavirus HKU1, Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Parainfluenza 4, Influenza A H3, Rhino/Enterovirus, Adenovirus, Respiratory Syncytial Virus (RSV) A/B, Human metapneumovirus (HMPV) A/B, Bocavirus, Mycoplasma pneumoniae, Legionella pneumophila, Bordetella pertussis, Corona COVID-19.

* = Norovirus G1, Norovirus G2, Rotavirus, Adenovirus, Astrovirus, Sapovirus.

* = CMV, Adenovirus, Herpes Simplex Virus (HSV) 1, Herpes Simplex Virus (HSV) 2, Varicella Zoster Virus (VZV), Parechovirus, Parvovirus, Astrovirus, 16s, 18s, Toxoplasma.

Undet = undetected.
movement disorder on a background of enterovirus encephalitis that significantly affected the basal ganglia, which was expected to become more pronounced over time. It was difficult to determine based on clinical assessment whether an ongoing neuroinflammatory process was contributing to his evolving dyskinesias and hypertonia, and given the recent sharp rise in CD3+ T cells, to 800 cells/µl, a 1-week trial of 2-mg/kg prednisolone was undertaken to treat possible immune reconstitution inflammatory syndrome. This did not significantly improve his movement disorder.

Virus recovered from the CSF was found to be sensitive in hep2 cell plaque reduction assays to fluoxetine hydrochloride, demonstrating complete inhibition at 25 µM. While enteroviruses have shown susceptibility to favipiravir, p MCPA virus, and ribavirin, all three drugs were toxic to cells, preventing sensitivity testing of this isolate (1–3). The case was discussed in multidisciplinary team (MDT) fora, including a combined Neurology and Infectious Diseases MDT meeting, which provided consensus support for the novel approach to management of such complex cases. Combination therapy was continued despite lack of in vitro evidence of sensitivity to favipiravir in view of a clinical response.

After 8 weeks of therapy, his neurological signs stabilised, with some ongoing dystonic posturing, but no prolonged dystonic events. He had excellent immune recovery with 1,420/µl CD3+ cells, 1,190/µl CD4+ T cells, normal naive T cells, PHA and gamma chain expression, and expected levels of gene marking. He was discharged 4 months after gene therapy. After 8 weeks of therapy, his neurological signs stabilised, with some ongoing dystonic posturing, but no prolonged dystonic events. He had excellent immune recovery with 1,420/µl CD3+ cells, 1,190/µl CD4+ T cells, normal naive T cells, PHA and gamma chain expression, and expected levels of gene marking. He was discharged 4 months after gene therapy.

Discussion

This is the first case report of combined therapy with favipiravir, fluoxetine, and high-dose IVIg in the context of severe enterovirus encephalitis in an immunocompromised host. The lack of any approved antiviral treatments for enterovirus infection presents a particular therapeutic challenge in immunocompromised individuals. The use of high-dose IVIg in chronic enteroviral meningitis has previously been documented, as has fluoxetine as an adjunct to high-dose IVIg in a patient with X-linked agammaglobulinemia (2, 4). Favipiravir has shown in vitro activity against enteroviruses; however, to our knowledge, there have been no reports of its use in enteroviral Central nervous system (CNS) infection (5).

Favipiravir is a novel antiviral compound that was developed in 2002 as an inhibitor of influenza virus replication (5). It works by selectively and potently inhibiting the RNA-dependent RNA polymerase (RdRP) of RNA viruses, inducing mutagenesis and resulting in a loss of viral fitness. RdRP domains are not present in human cells, however, are conserved among RNA viruses, and when assessed against a panel of enterovirus-D68 strains, they proved to be a weak inhibitor of in vitro replication of enterovirus (3). Previous in vitro assessment confirmed the mechanism of action of favipiravir by demonstrating that an S121N mutation in the finger subdomain of the 3D polymerase of the EV-A71 strain of enterovirus conferred resistance to favipiravir (6). Low levels of the active metabolite have been detected in the brain; however, assessment of this is limited and has only been conducted in mice (7). The drug is approved in Japan for treatment of non-complicated infections with influenza virus; however, it is also active against other RNA viruses including Ebola virus. Mixed evidence of clinical benefit exists in coronavirus disease 2019 (COVID-19), with shorter times to clinical improvement; however, there was no significant difference in mortality in two meta-analyses comparing treatment with and without favipiravir in patients with COVID-19 (8, 9). Additionally, a spectrum of difference in adverse events was seen between the two groups, ranging from both more and less adverse events in the favipiravir group compared to the control to no difference between the favipiravir and control group.

Treatment for this patient required approval from the hospital DTC, as favipiravir is unlicensed in the United Kingdom, where treatment took place. The drug was imported from Japan where it is licensed for influenza A and B in adults. A lack of availability of p MCPA virus, toxicity associated with ribavirin, and a cumulative experience at our tertiary centre in using favipiravir in RNA virus infections in immunocompromised hosts favoured the selection of favipiravir in this treatment regimen. Dosing has previously been established for adult Japanese patients infected with influenza and body weight-based dosing proposed in a trial in children infected with Ebola, which informed the dosing in this patient (10, 11). The drug holds a favourable safety profile, with the most frequently reported adverse events including mild to moderate diarrhoea and a decrease in neutrophil count. No adverse effects were reported in this patient, with monitoring throughout treatment via regular physical assessments screening for rash and gastrointestinal side effects and measurement of liver function tests, full blood counts, and electrolytes, all of which were within normal range (12).

In immunocompetent individuals, 90% of non-polio enterovirus infections are asymptomatic or mild febrile illnesses. Infection can also manifest more severe disease, for example, viral meningitis, accounting for between 48% and 95% of cases where a causative virus is identified (13). Conversely, infections in immunocompromised hosts including primary immunodeficiency, neonates, and post-HSCT result in more serious disease often of a chronic nature ranging from meningoencephalitis, dermatomyositis, hepatitis, and/or...
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The course of disease in the immunocompromised host tends to be slow and progressive with periods of remission and relapse. Meningoencephalitis specifically features a range of neurological symptoms including ataxia, loss of cognitive skills, and paraesthesias.

Immune reconstitution inflammatory syndrome (IRIS) describes an excessive inflammatory response to infection occurring during immune reconstitution after a period of immunosuppression. The history of self-limiting facial palsy may have been indicative of enterovirus infection, with the subsequent neurological symptoms being a manifestation of IRIS. However, a short course of corticosteroids, the most frequently used agent for the treatment of IRIS, did not result in resolution of symptoms.

Most transplant centres do not routinely screen for enterovirus infection pretransplant or posttransplant. Given the devastating effects of infection in the immunocompromised, as highlighted here, it raises the question of whether screening for enterovirus should become a standard of care. Without any definitive treatments or approved antiviral therapies for enterovirus, screening may not provide any significant additional benefit to morbidity and mortality. However, prompt initiation of novel treatments in post-HSCT and gene therapy infections may mitigate neurological deterioration and control the virus before recovery of immune function.

Besides the possibility that this novel therapeutic regimen effectively treated this patient's enterovirus infection, it is conceivable that this child's improvement may have been due to immune recovery over time. While there is a lack of literature on the natural history of enterovirus in X-SCID patients treated with gene therapy, an evaluation of 64 T cell-depleted adult allograft recipients found no correlation between immune recovery and the occurrence of enterovirus infections, in particular, no difference in the median estimate of CD4+ T-cell count and absolute lymphocyte count posttransplant in those with and without enterovirus infections.

Given that the course of IRIS is to improve over time, despite the lack of immediate symptom improvement with steroids, IRIS may also be another explanation for the constellation of neurological symptoms seen secondary to the infective insult. It is extremely challenging to determine the contribution of infection and inflammation in the context of IRIS and therefore whether anti-infectives or anti-inflammatories are to be prioritised. Given the diagnostic ambiguity, often, both will be required.

Although it is difficult to objectively assess the family's satisfaction with this novel antiviral treatment regimen, given the neurologic sequelae of this patient's disease, the family was happy to be offered this new treatment and was informed and satisfied to continue with the treatment regimen.

This case highlights the importance of considering enterovirus encephalitis in immunocompromised patients presenting with both acute and chronic neurological signs, as well as developmental regression. The novel therapy regimen of favipiravir, fluoxetine, and high-dose IVIg was associated with neurological improvement and, given the low risk of toxicity, is worth consideration on a case-by-case basis and warrants further investigation.

**Data availability statement**

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

**Ethics statement**

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

**Author contributions**

KC and CB: preparing manuscript. KC, IC, MK, LG-G, AB, JB, CB: patient management, providing diagnostic and treatment results. DK, JM: providing diagnostic and treatment results. All authors contributed to the article and approved the submitted version.

**Funding**

All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. JB is supported by the Wellcome Trust. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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