6 Enterovirus-Associated Meningoencephalitis and Enteroviruses in Patients with Acute Encephalitis

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Abstract

Enteroviruses are from the family of Picornaviridae, consisting of hundreds of serotypes, all having single positive-stranded RNA genome. The Enterovirus group comprises of 12 species, including 4 human species: A to D. Encephalitis and meningoencephalitis are infrequent presentations of enteroviral infection, but various enterovirus serotypes, coxsackievirus serotypes, and echovirus serotypes are reported in epidemics in the Southeast Asia region and some European countries. Enteroviruses mostly enter via faeco-oral routes and present with asymptomatic or mild diseases. However, they are also known to present as biphasic prodromal disease, with neurological involvement often beginning as invasion in the anterior horn cells, or even as progression to the brainstem, cerebellum, midbrain, or motor cortex, causing paralysis from neuronal death. More so, enterovirus encephalitis can present as fever with headache, altered sensorium, acute onset muscle flaccidity, hyporeflexia, meningeal signs, and myoclonic jerks. The diagnosis of enteroviral neurological illness is 'definitive' when it is detected by cerebrospinal fluid polymerase chain reaction or culture, along with detection by polymerase chain reaction from throat, rectal

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H. Sami et al. (eds.), *Viral and Fungal Infections of the Central Nervous System: A Microbiological Perspective*, https://doi.org/10.1007/978-981-99-6445-1_6

swabs, and serum. Diagnosis is 'probable', if enterovirus is detected in polymerase chain reaction analysis of throat and rectal swabs. If it is detected in either throat or in rectal swab polymerase chain reaction tests, it is denoted as 'possible' enterovirus infection. There is no definitive treatment for enteroviruses, although, intravenous immunoglobulins and ribavirin have shown some promising outcomes in patients diagnosed with enteroviral encephalitis.

Keywords

Enteroviruses · Encephalitis · Meningoencephalitis · Cerebrospinal fluid

6.1 Pathogens

6.1.1 Overview of Enteroviruses

The genus, *Enterovirus*, EV, from the *Picornaviridae* family, is classified by the ICTV, International Committee on Taxonomy of Viruses, into a total of 12 species, of which seven are notable human pathogens (Lei et al. 2016). Human infection-associated EVs comprise of coxsackieviruses (CV-A, CV-B), numbered enteroviruses (EV-A71, EV-D68, etc.), echoviruses (ECV), human rhinoviruses (HRV), and even polioviruses (PV) (Jubelt and Lipton 2014) (Table 6.1).

These ubiquitous RNA-viruses are often times involved in human infections of varying spectra; some with limited time frames of illness, and some presenting as fulminant, non-reversible changes in different organs or systems. These viruses can cause diseases ranging from neurological illnesses, including paralysis, inflammatory reactions, and even morbid conditions contributing to death. Enteroviruses have the potential to cause outbreaks of poliomyelitis disease. Moreover, they tend to cause morbid conditions in the form of encephalitis, meningitis, and vesicular stomatitis in susceptible individuals. But these viruses may be responsible for simpler conditions too, such as the common cold (Nikonov et al. 2017; Rotbart 2000).

6.1.2 Viral Structure

The genomic component of an EV comprises of a positive-sense, single-strand ribonucleic acid of up to 8000 nucleotides with an open reading frame- ORF of a 5′ untranslated region- UTR and a 3'-UTR end (Table 6.2).

The 3′-UTR has a poly (A) tail (pseudoknot) and the 5′-UTR has a 40S ribosome subunit-binding site, known as the IRES (internal ribosomal entry site), for cap-independent translation. The polyprotein precursor with its regions: P1, P2, and P3, is encoded by the ORF (Fig. 6.1). In the initial phase, as an EV infects a cell, viral 3C proteinase cleaves between P2 and P3 of this precursor protein, while 2A proteinase cleaves at the P1-P2 junction (Racaniello 2016). Eventually, mature

Table 6.1 Picornaviridae classification (depiction only of clinically relevant genera and species) (Simmonds et al. 2020; Zell et al. 2017 Viral structure

Order: Picronavirales ⇒ FAMILY: Picornaviridae (i.e., Picornaviruses)							
Subfamily	Caphthovirinae		Ensavirinae			Heptrevirinae	Paavivirinae
Genera	Aphthovirus	Cardiovirus	Enterovirus			Hepatovirus	Parechovirus
SPECIES (including subspecies and genotypes)	**Foot and mouth disease viru**, etc.	**Cardioviruses** A–F	**Enterovirus A:** Coxsackievirus A2–8, A10, A12, A14, A16; enterovirus A71, A76, A89–92, A99, A114, A119–125 **Enterovirus B**: Coxsackievirus B1–6, A9; Echovirus 1–9, 11–22, 24–27, 29–33; Enterovirus B69, B73–75, B77–88, B93, B97, B98, B100, B101, B106, B107, B110–114; **Enterovirus C:** Poliovirus 1,2,3; Coxsackievirus A1, A11, A13, A17–22, A24; Enterovirus C95, C96, C99, C102, C104, C105, C109, C113, C116–118 **Enterovirus D:**	**Enterovirus E:** (E1–5); Enterovirus F: (F5–7); **Enterovirus G:** (G1–20); **Enterovirus H:** (H1); **Enterovirus I:** (I1, I2); **Enterovirus J:** (J1, J103, J108, J112, J115, J121); **Enterovirus K:** (K1, K2); **Enterovirus L:** (L1);	**Rhinovirus A:** (A1–2, A1B, A7–13, A15–16, A18–25, A28–34, A36, A38–41, A43, A45–47, A49, A51, A53–68, A71, A73–78, A80–82, A85, A88–90, A94, A96, A100–108); **Rhinovirus B:** (B3–6, B14, B17, B26–27, B37, B42, B48, B52, B69–70, B72, B79, B83–84, B86, B91–93, B97, B99–104); **Rhinovirus C:** (C1–51, C54–57)	**Hepatovirus A** (hepatitis A virus); **Hepatoviruses** B-I	**Parechovirus A:** Human parechovirus 1–18; **Parechovirus B:** Ljunganvirus 1–6; **Parechoviruses C-F**

(continued)

Table 6.1 (continued)

Order: Picronavirales ⇒ FAMILY: Picornaviridae (i.e., Picornaviruses)							
Subfamily	Caphthovirinae		Ensavirinae			Heptrevirinae	Paavivirinae
			Enterovirus D68, D70, D94, D111, D120; Human rhinovirus 87;				

Table 6.2 Genomic components of Enteroviruses (and other Picornaviruses)

Viral genome	(+) sense; single-stranded RNA (non-segmented); 6.7 to 10.1 kb
Virion	30–32 nm; icosahedral capsid; non-enveloped

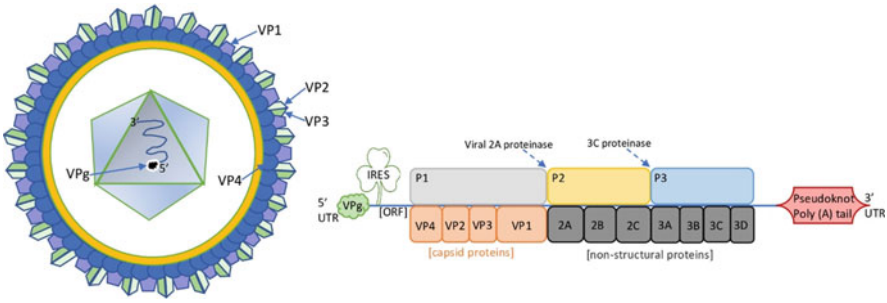

Fig. 6.1 Basic Enterovirus Virion and Genome

EV proteins are processed from this polyprotein precursor, consisting of structural capsid proteins: VP1, VP2, VP3, VP4, non-structural proteins: 2A, 2B, 2C, 3A, 3B, 3C, and 3D. The modulation of proteins involved with apoptosis, innate immunity, poly-adenylation, ribonucleic acid processing and translation is aided by 2A and 3C proteinases, in particular, which in turn, profoundly, effects the infected host cells (Kräusslich et al. 1987; Lei et al. 2010, 2002; Wang et al. 2013; Weng et al. 2009).

6.1.3 Epidemiological Profile

Non-polio enteroviruses (NPEV) may give rise to an array of syndromes, ranging from common cold, haemorrhagic conjunctivitis, hand-foot-mouth disease, herpangina, meningitis, myocarditis, neonatal sepsis, as well as paediatric fever-rash illnesses. This chapter provides a well-constructed insight on non-polio enteroviral CNS infections; encephalitis and meningitis, in particular.

Meningitis and encephalitis are most commonly caused by viral aetiologies, out of which NPEV remain the prominent cause (Michos et al. 2007; Romero 2002; Rotbart 2000). They have been suggested to cause 10% of viral encephalitis cases (Calleri et al. 2017). NPEVs are also responsible for 50–80% aseptic meningitis cases in adults (Han et al. 2016). Compared to meningitis of other viral or bacterial aetiologies, EV meningitis often has a milder course, with occasional serious illness reserved for the early childhood populations, and those with weakened immune systems.

Amongst non-polio enteroviruses, several subspecies of Enterovirus A (e.g., EV-A71, CV-A10), B (e.g., CV-A9, CV-B5, ECV-6, ECV-9), C (e.g., CV-A11, CV-A13), and D (e.g., EV-D68) have been implicated in CNS infections, resulting in a variety of neurological complications, namely, aseptic meningitis, acute flaccid paralysis, and encephalitis (Table 6.3).

Table 6.3 Neurological infections caused by NPEVs (B'Krong et al. 2018; Fan and Liu 2019; Messacar et al. 2018; Pallansch et al. 2013; Sun et al. 2019; Suresh et al. 2018)

CNS infection	Commonly implicated serotypes	
Aseptic meningitis	Enterovirus A: Coxsackievirus A2, A5–7, A10, A16; Enterovirus A71 Enterovirus B: Coxsackievirus B1–6, A9; Echovirus 1–4, 6, 7, 9, 11–21, 24, 25, 27, 29–31;	Enterovirus C: Coxsackievirus A11, A13, A17, A22, A24; Enterovirus D: Enterovirus D68, D70
Encephalitis	Enterovirus A: Coxsackievirus A2, A6, A10, A16; Enterovirus A71 Enterovirus B: Coxsackievirus B1, B2–5, A9; Echovirus 3–7, 9, 11, 13, 14, 16–19, 21, 24, 25, 27, 30, 33;	Enterovirus C: Coxsackievirus A11, A13; Enterovirus D: Enterovirus D68, D70
Acute flaccid paralysis	Enterovirus A: Coxsackievirus A2–7, A10, A12, A14, A16; Enterovirus A71, A76, A90; Enterovirus B: Coxsackievirus B1–6, A9; Echovirus 1–7, 9, 11–22, 24–27, 29–33; Enterovirus B73–75, B77, B79–81, B85–88, B93, B97, B100, B106, B107	Enterovirus C: Coxsackievirus A1, A11, A13, A17, A20–22, A24; Enterovirus C96, C99, C109; Enterovirus D: Enterovirus D68, D70, D94

Enteroviral transmission occurs almost exclusively via faeco-oral routes (Nikonov et al. 2017; Rotbart 2000). There are, however, reports of person-to-person transmission of enteroviruses via respiratory droplets and also via contact with enterovirus-contaminated objects. EVs reside in the gut of infected persons, and are shed in their faeces. They are quite stable and capable of living in environments outside of the human body as well. Contact with faecal matter can lead to the contamination of hands and surfaces with enteroviruses. Viral particles that are ingested and/or in contact with mucosal membranes lead to EV infection. Improved hand hygiene can thereby reduce the spread of enteroviruses (Romero 2002; Rotbart 2000).

Infected individuals can be asymptomatic for long periods, during which enterovirus shedding potentiates risks of giving rise to epidemics in different time frames and countries, making it difficult to trace the initial source (Nikonov et al. 2017). Even while enterovirus infections are often contracted, very few of those infected go on to acquire meningitis or encephalitis. Also, there is very little chance of close contact-associated spread of EV meningitis. Enteroviral infections in general may occur on a perennial basis in the subtropics or tropics, and in temperate climates they tend to have seasonal surges during the summers or early autumns (Romero 2002; Rotbart 2000). Infected populations are predominantly children and infants, with epidemic or sporadic occurrences. Even though numerous enterovirus serotypes can

cause encephalitis or meningitis, only a few are actually widespread (Greenberg 2003).

6.2 Etiopathogenesis

6.2.1 Routes of Central Nervous System Invasion

Enteroviruses which cause meningoencephalitis most commonly infect the human through the faecal-oral route and rapidly replicate in the gastrointestinal tract. However, there are few exceptions like for example enteroviruses, EV-D68, they spread via respiratory secretion and can cause respiratory infection. After initially infecting the first exposed area, the viruses easily gain access to the central nervous system via various pathways, which are not mutually exclusive (Rhoades et al. 2011; Huang and Shih 2015).

6.2.1.1 Through the Bloodstream

First, the neurotropic enteroviruses take the course of bloodstream to reach the CNS. Normally, there is a highly selective semipermeable blood brain barrier (BBB) which restricts the viral particle spread from brain's blood vessels to the CNS. However, if the central nervous system's microvascular endothelial cells (BMECs) are infected the integrity of the BBB is largely compromised. The cytokines which are locally produced during the time of infections also poses a big threat to the BBB.

6.2.1.2 Through the Peripheral Circulating Immune Cells (Trojan Horse Route)

In this route, the immune cells which are circulating peripherally carry intracellular viruses (Tabor-Godwin et al. 2010). As a well-established fact, that brain has an active immune surveillance system comprising numerous non-specific leukocytes like lymphocytes and phagocytes to be involved into the meninges and cerebrospinal fluid (Forrester et al. 2018). Additionally, it has been demonstrated that cerebrospinal fluid (CSF) has an appropriate number of trafficking mononuclear cell types, with T cells accounting for the majority 90%, B lymphocytes for a minor 5%, monocytes for the remainder, and dendritic cells for the smallest percentage, i.e., less than 1% (Ransohoff and Engelhardt 2012). These cells become vehicles for viruses to enter the CNS after being infected. The enterovirus is released from myeloid cells upon entrance into the CNS, where it then infects the neuroglial cells and neurons. Recent studies have shown that the sialomucin membrane protein hPSGL1, which is produced on the surface of leukocytes, can bind to EV-A71, exhibiting leukocytic infection (Nishimura et al. 2013).

6.2.1.3 Through Nerves in the Periphery Via Retrograde Axonal Transport and Trans-Synaptic Propagation

Peripheral nerves, which are accessible to enteroviruses through retrograde axonal transport and trans-synaptic propagation, are another possible route for them to enter

the CNS (Gromeier et al. 1996; Chen et al. 2007; Ong et al. 2008). Transport via axons is an important cellular process in neurons which is required for the movement to and from the cell body of synaptic vesicles, lipids, proteins, and other organelles including mitochondria, lysosomes, endosomes, and autophagosomes. Few neurotropic viruses have the ability to hijack the retrograde axonal transport to directly invade and infect the central nervous system. The viral particles which are endocytose in the terminal end of axon are moved in retrograde direction through dynein-mediated vesicular transport towards the cell body without uncoating (Ohka et al. 2009). The event of uncoating takes place upon arrival of the motor neuron at the cell body (Chen et al. 2007; Ong et al. 2008; Hixon et al. 2017). The ability of EV-A71 to directly infect the brainstem via cranial nerves has been shown, which is intriguing and implies that for CNS infiltration, not only does the virus use the motor portions of spinal nerves, but also the cranial nerves (Tanet al. 2014).

6.2.2 Cell Receptors for Virus Entry

There are numerous entry mechanisms and receptors used by enteroviruses to invade and infect the host cell. EnteroVirus-71 has been conclusively shown to use several receptors, including P-selectin glycoprotein ligand-1, sialylated glycans, and Scavenger receptor B2 (Nishimura et al. 2013, Yamayoshi et al. 2014, Yang et al. 2015). Some of the enteroviruses are capable of using multiple receptors to invade the host cell. The first barrier for the virus's entrance is determined by the receptor expression on the targeted cells. An infection may become less likely during differentiation, as the amount of viral receptor diminishes. This is what was concluded in a recent study that specifically linked reduced coxsackievirus and adenovirus receptor (CAR) expression in differentiated-primary neurons, to a decrease in infection (Ahn et al. 2008).

6.2.3 Tropism

Tropism is distinct for each enterovirus and is mainly determined by a number of host and viral factors. As elaborated above, neurotropic enteroviruses invade CNS and cause neurological disorders. There is evidence of viral dissemination into the CNS sporadically. There is also evidence that interferons (IFN) which are the innate immune antiviral activities are essential for virus tropism (Wessely et al. 2001; Ida-Hosonuma et al. 2005). EV-A71 invades the nervous system and the areas infected are very distinct. Encephalitis of the brainstem is the commonest neurological presentation of EV-A71 infection. The lesions produced by the virus are profoundly found in the brainstem and is located in various parts of medulla oblongata like the ventral, medial, and caudal areas. (Kao et al. 2004). The spinal column, cerebellum, and cortex may also present with a few lesions. In severe EV-A71 infection, the CNS exhibits significant histo-morphological changes that are characterized by inflammatory damage that specifically cause heart failure and

neurogenic pulmonary oedema. It has been determined that the medullary neurons are liable for the development of neurogenic pulmonary oedema (Davison et al. 2012). According to recent investigations in postmortem, EV-A71 can also affect neurons and produce neuronal degeneration, triggering inflammatory responses in the afflicted area and resulting in encephalitis (Yan et al. 2000; Khong et al. 2012; Yao et al. 2012; Feng et al. 2016). It is interesting to note that while EV-A71 can infect neurons, it seems to primarily target astrocytes and neural progenitor cells. The ability to undergo mitosis, that could prove essential for virus replication, is a shared characteristic for the two cell types (Yu et al. 2015). Cognitive, learning, memory, and other such functions depend on neural progenitor cells which are thought of as the cells which give rise to neuroglial and neuronal cells. Therefore, the loss of neural progenitor cells brought on by an EV infection may result in long-term or permanent neurological problems (Chang et al. 2007).

6.2.4 Enteroviruses and Autophagy

Enteroviruses have been shown to greatly benefit and induce the degradation at cellular levels. This process is commonly known as autophagy (Huang et al. 2009; Suhy et al. 2000, Wong et al. 2008). They utilize the autophagosome membrane for replication of the virus as a scaffold. In an experimental work, scientists inferred that induction of autophagy was seen in rat-primary neurons due to raised viral replications (Yoon et al. 2008). Autophagy plays a vital role in preventing neuronal cellular damage (Alirezaei et al. 2015).

6.2.5 Persistent Infection

Although enteroviruses are proved to be cytolytic and the caused disease by the infection is short-lived, numerous studies are now showing association with lifelong disorders which are permanent. The cause of this is not clear yet but is hypothesized that this persistence of enteroviral infection may occur due to the presence of infected viral RNA and protein in the affected tissues at stages of disease after acute infection (Chapman and Kim 2008). Due to lack of proofreading capacity in RNA polymerases, the enteroviruses have high mutation rates thereby generating a variety of mutants to invade the immune system. As CNS is inaccessible to immune surveillance, it makes it vulnerable to persistent infection.

6.3 Diagnosis

6.3.1 Presenting Features

Encephalitis, meningitis, myelitis, and neuritis are a few of the important clinical presentations of enteroviral invasion of the central nervous system. In general terms, encephalitis refers to brain parenchymal inflammation characterized by signs of neurologic impairment in the form of clinical, laboratory, or imaging findings. Aseptic meningitis, on the other hand, refers to sudden development of meningeal warning signs, with/without fever, and pleocytosis on CSF biochemistries, as well as negative bacterial cultures, along with no evidence of parenchymal involvement. Owing to the structure of the nervous system, patients with meningitis generally always have concomitant involvement of the brain parenchyma (meningo-encephalitis), and in some cases, there may also be involvement of the spinal cord (encephalomyelitis) or nerve roots (encephalomyeloradiculitis). The individual pathogen and the host's immunological status have a significant impact on the clinical spectrum of neurologic dysfunction as well as the prognosis (Mandell et al. n.d.) In spite of an extensive workup, the cause of encephalitis remains elusive in up to approximately 60% of the population. Enterovirus is the most common cause of aseptic meningitis in children as well as adults; however, the data regarding enteroviral encephalitis in adults vis à vis the presentation and outcomes is sparse (Fischer et al. 2022; Glaser et al. 2003; Hasbun et al. 2017). Most of the reported cases of enteroviral encephalitis in adults are centred around outbreaks involving the paediatric population, with common culprits implicated including echovirus 30 and enterovirus-A71 (Peigue-Lafeuille et al. 2002; Sapkal et al. 2009; Solomon et al. 2010), and cases are generally diagnosed and reported retrospectively.

There are two known types of infection-related encephalitis: primary and post- or para-infectious. Direct central nervous system invasion plus neuronal damage, which frequently also affects the grey matter, conduces to a primary encephalitis. While the symptoms of a post- or para-infectious encephalitis are similar to those of a primary encephalitis, these infections do not directly invade the CNS, and instead, the neurologic effects are a result of the host's immune response, which frequently affects the white matter (Lewis and Glaser 2005).

Data shows that the onset of enteroviral encephalitis may be gradual or abrupt, and there may be a brief prodrome of fever and chills, with severe headache being the predominant complaint. Meningismus may be present, varying from mild to severe, depending on the extent of meningeal involvement. Kernig and Brudzinski signs are present in only about one-third of patients. Other symptoms may include photophobia, nausea, vomiting, diarrhoea, and myalgia (Peigue-Lafeuille et al. 2002). Pharyngitis and other symptoms suggestive of upper respiratory tract infection are commonly present. Quite often, there may be a biphasic pattern of presentation, resembling poliomyelitis, with an initial prodromal phase comprising of fever, upper respiratory tract symptoms, and myalgias, a phase of defervescence of symptoms for a few days followed by an abrupt relapse with the trifecta of fever, headache, and meningism (Bernit et al. 2004).

General physical examination may herald a few clues, for example the presence of herpangina, or hand-foot-and-mouth disease may indicate coxsackievirus; however, most often the findings would be too non-specific for the clinician to clinch a specific viral organism.

The neurologic manifestations of enteroviral encephalitis may be broadly considered under four headings: behavioural alterations (i.e., agitation, altered mentation, hallucinations, personality changes, psychosis, etc.), cognitive decline (e.g., acute memory problems), focal CNS conditions (i.e., anomia, dysphasia, hemianopia, hemiparesis, etc.), and seizures, depending on the site of involvement (Steiner et al. 2005). The most frequent focal neurologic manifestations include ataxia, aphasia, hemiparesis, myoclonus, cranial nerve palsies, and seizures. Involvement of centres for autonomic control may manifest as a loss of vasomotor tone and temperature control, and rarer presentations include the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or diabetes insipidus owing to hypothalamic dysfunction. Other presentations may include brainstem involvement or even involvement of the anterior horn cell, resulting in acute flaccid paralysis (Mandell et al. n.d.).

A severe, and often fatal form of brainstem encephalitis (rhombencephalitis) is known to be caused by enterovirus-A71 and, occasionally, other EV serotypes. It is also accompanied by secondary cardiac symptoms, such as neurogenic pulmonary oedema and cytokine storm (Hamaguchi et al. 2008; Huang et al. 1999). Countries of the Asia-Pacific Rim belong to one of the hotspots for EV-A71 encephalitis, with records of multiple large outbreaks over the past 10–15 years (Solomon et al. 2010). Principally affecting toddlers and infants, typically neurological manifestations are preceded by hand-foot-and-mouth disease or herpangina. This is followed by the development of progressive myoclonic jerks, tremors, and ataxia; mortality is reported to be as high as 19% (Chan et al. 2003; Ho et al. 1999).

Those who have immunodeficiencies (whether congenital or acquired) have shown a notable predisposition for the acquisition and development of serious EV infections which can present as acute or even chronic infection involving multiple organ systems. Such individuals have been described as having a wide range of CNS consequences, like brainstem involvement, cerebellar manifestations, cranial nerve palsies, encephalopathy, extrapyramidal defects, frontal dementia, and localized (focal) cortical involvement. There is a high prevalence of cochlear nerve involvement when it comes to cranial nerve palsies in these patients (Wagner et al. 2021). Echovirus has also commonly been implicated in the setting of encephalitis in patients with hypogammaglobinaemia (Prentice et al. 1985).

6.3.2 Differential Diagnosis

The constellation of signs and symptoms associated with viral encephalitis and meningitis, including fever, nuchal rigidity, and headache is not specific, and the various differentials include bacterial meningitis, cerebritis, brain abscess, subdural and epidural empyemas, and septic cerebral venous or sinus thrombosis, which

should accordingly be ruled out by imaging and further testing. The most important differential to rule out would be bacterial meningitis, as some cases of inadequately treated bacterial meningitis patients may resemble viral encephalitis, especially with regards to the CSF parameters (Steiner et al. 2005).

Viral aetiologies of encephalitis in immunocompetent patients typically include Epstein–Barr virus, herpes simplex virus, and varicella-zoster virus; arboviruses are associated with epidemics of encephalitis. Other differentials to consider would be leptospirosis, borreliosis, Lymes disease, lymphocytic choriomeningitis virus, and acute human immunodeficiency virus infection, which account for most of the remaining cases of infectious aseptic meningitis (Glaser et al. 2003).

6.3.3 Laboratory Diagnostics

Pleocytosis and other inflammatory alterations in the cerebral fluid, along with EV detection by polymerase chain reaction (PCR) analysis, are used for diagnosing enteroviral encephalitis and meningitis (Logan and MacMahon 2008). EV-induced CNS infections, however, may be difficult to diagnose in the presence of unusual clinical manifestations, particularly among elderly persons, as well as in circumstances with lack of cerebrospinal fluid pleocytosis (Ihekwaba et al. 2008; Valcour et al. 2008; Wang et al. 2014). Concurrent testing from locations other than the cerebrospinal fluid may help with diagnosis; however, EV is produced by around 7–8% of healthy controls during viral seasons and is shed from various body sites for several weeks after infection has cleared up (Table 6.4). Moreover, genotyping of enteroviruses with phylogenetic analysis is already a common practice, particularly during epidemics (Savolainen-Kopra et al. 2011; Torok et al. 2017). Enteroviruses spread through the faeco-oral route or less commonly, through respiratory routes, and symptoms can appear anywhere post the incubation period of 3–21 days (Harvala et al. 2018).

Clinical samples should be collected in accordance with clinical symptoms (Table 6.5). Ideally, they should be transported directly to the lab in viral transport media (VTM) and if need be, stored at 4 °C for up to 24 h.

6.3.3.1 Cerebrospinal Fluid (CSF) Biochemistry

To obtain cerebrospinal fluid for a definite diagnosis, a lumbar puncture is carried out. The CSF biochemical analysis typically displays normal glucose levels; although reduced glucose levels may be seen in 15% of patients (Greenberg 2003). White blood cell (WBC) counts in the CSF of aseptic meningitis cases are somewhat higher. Lymphocyte and other mononuclear cell predominance (pleocytosis) is found in more than 66% of infections (Table 6.6). However, in some patients, abundant polymorphonuclear leukocytes in the CSF may also be detected within the initial 6–48 h. Also, whilst the level of protein is normal to slightly elevated, the level of glucose may occasionally be slightly lowered (Chia 2018).

Table 6.4 Laboratory Techniques to diagnose EV Meningitis and/or Encephalitis (Harvala et al. 2018; Storch 2000; Ye et al. 2013)

Laboratory techniques	Comments
Cerebrospinal fluid (CSF) biochemistry	Definitive diagnosis may be obtained by CSF analysis plus CSF polymerase chain reaction (PCR)
Electron microscopy	Reserved for research and further morphological identification/characterization
Immunohistochemistry	Reserved for research studies
Molecular methods:	
i. In situ hybridization	Reserved for research studies
ii. Nucleic acid sequence-based amplification (NASBA)	Up to 100% sensitivity
iii. Reverse transcription-polymerase chain reaction (RT-PCR) [nested, multiplex, probe-based, etc.]	PCR has higher diagnostic value than EV culture;
iv. RT-PCR is more sensitive (95–100%) than culture; ≥ 97% specific	
v. Real-time RT-PCR (rtRT-PCR)	Sensitivity of up to 100%; specificity of ≥96%
Serology:	Routine serology testing for acute EV infection diagnosis is NOT recommended due to subpar EV detection standards of most of these tests
i. Antigen detection	
ii. Enteroviral IgM antibodies	
iii. Enzyme immunoassays	
iv. Enzyme-linked immunosorbent assay (ELISA)	
v. Fluorescent antibody staining	
vi. Immuno-peroxidase antibody staining	
vii. Neutralization assays	
Viral culture (Cell/tissue culture)	NOT sensitive (~30–70%); NOT for routine diagnostic use, but may be used for further EV characterization at national level

Table 6.5 Advised Sample types for EV Meningitis/Meningoencephalitis Laboratory Diagnosis (Ye et al. 2013)

Clinical Sample	Remarks
Cerebrospinal fluid (CSF)	Viral RNA in CSF is detectable by PCR in almost all EV meningitis cases, but detection is inconsistent in EV encephalitis cases
Other sterile sites: Serum/urine/ vesicular fluid/collection at autopsy	More reliable than non-sterile sites
Respiratory sample; throat/nasal swabs; Faeces sample	There is prolonged viral excretion in faecal samples and throat, but its detection does not directly imply any etiological link, i.e., may merely imply coincidental carriage

Table 6.6 Typical CSF Findings in EV Aseptic Meningitis and/or Encephalitis (M. Tille 2021)

	Findings	Normal Ranges
Glucose	Normal/slight ↓ [30–45 mg/dL]	45–100 mg/dL [glucose CSF: Serum of 0.6 or 50–70% of normal blood glucose value]
Leukocytes (mm^3)	2–1000	0–5
Opening pressure	Normal/slight ↑	< 180 mmH_2O
Predominant cell type	↑ lymphocytes	None
Protein	Normal/slight ↑ [50–100 mg/dL]	15–50 mg/dL

6.3.3.2 Electron Microscopy

Electron microscopy (EM) is reserved mostly for research purposes in highly professional and designated research facilities. Morphological characteristics can be discovered and studied using EM or transmission electron microscopy as the basis for virus identification using thin-section, negative staining, or cryo-EM technique (with cell or brain tissue specimens). Unfortunately, it has a low sensitivity and needs at least 10^6 virions per milligram of specimen to be visible under a microscope (Hussin et al. 2022).

6.3.3.3 Immunohistochemistry

Immunohistochemistry and other histology-based techniques are mostly reserved for research studies. For instance, immunohistochemistry of encephalitic brain matter may be done, using different antibodies to look for significantly stained cytoplasm of affected neurons or microglia. Patented anti-CV-B polyclonal antibodies, EV-A71 mouse monoclonal antibodies, and mouse monoclonal antibodies to conserved EV VP1 are some of the antibodies that may be used (Dourmashkin et al. 2012).

6.3.3.4 Molecular Methods

Polymerase Chain Reaction—Culture identification of enteroviruses in meningitis or encephalitis are not sensitive (around 30%), because of low EV titres in cerebrospinal fluid. For EV meningitis and encephalitis, reverse transcription-polymerase chain reaction (RT-PCR) tests are much more sensitive (up to 100%) and over 94–97% specific (Chia 2018; Torok et al. 2017). Due to their sensitivity, specificity and quick turnaround time, RT-PCR and real-time reverse transcription-polymerase chain reaction (rtRT-PCR) tests targeting the 5′ non-coding regions should be employed for EV infection diagnosis. Yet, it is crucial to guarantee that the technique being used is regularly updated and can identify all types of enteroviruses. Every laboratory that conducts EV testing ought to be accredited (Harvala et al. 2018). It is quite effective at identifying EV RNA in CSF samples, with several studies reporting a 100% sensitivity with 97% specificity. To put it simply, the gold standard for diagnosing neurological enteroviral infections has been supplanted by EV RT-PCR since it has a far higher sensitivity than culture techniques (DeBiasi and Tyler 2004).

This test is authorized for the diagnosis of enterovirus meningitis, and results are available within 24 h. But in patients presenting with myalgic encephalomyelitis or chronic fatigue syndrome, only 30% have EV identified by PCR test of their blood specimens. The yield is less reliable for other bodily fluids such faeces samples, respiratory secretions, and blood (Chia 2018).

For other chronic EV infections, PCR is not thought to be sensitive. The likelihood of EV RNA or gene being detected in blood by PCR is minimal since the enteroviruses are swiftly eliminated from circulating blood. With specialized methods and repetitive testing, EV RNA can be discovered in almost 30% of whole blood specimens obtained from individuals presenting with persistent enteroviral infection (Chia 2018). Also, False-negative reports can sometimes be produced because of improper CSF handling or collection during late phases of EV illness (Ye et al. 2013).

Nucleic acid sequence-based amplification—Even though PCR tests are widely accessible at viral diagnostic institutes, nucleic acid sequence-based amplification (NASBA) is another molecular technique which can be explored as a good option for efficient detection and amplification of EV sequences in a variety of clinical samples, including cerebrospinal fluid (Fox et al. 2002). It is an in-vitro, isothermal, transcription-based amplification technique that has been converted into standardized kits for use in diagnostic labs where RT-PCR technology is not accessible. NASBA doesn't require certain specialized equipment like thermal cyclers (DeBiasi and Tyler 2004).

In situ hybridization—This technology is applied for EV positive-sense RNA detection in formalin-fixed paraffin-embedded specimens with the aid of designated probes. It enables anatomical localization and serotype determination of viruses (Laiho et al. 2015). In situ hybridization (ISH) techniques, when used alongside reverse transcription quantitative real-time polymerase chain reaction, may provide useful information on the EV infection and on potential targets for antivirals, paving ways for further discoveries (Salmikangas et al. 2020). Nucleic acid hybridization, however, is time-consuming and occasionally insensitive enough for diagnosis, for instance, in EV RNA detection in cerebrospinal fluid; they are yet to be standardized and reserved for research purposes only.

6.3.3.5 Serology

Only some numbered enteroviruses, including echoviruses- 6, 7, 9, 11, 30, and coxsackie viruses B1 through B-6 can be detected using serology-based diagnostic methods. These tests are unable to distinguish between the other known enteroviruses. It should be noted, a negative EV-serology test result does not always indicate that enterovirus is absent (Chia 2018). Serologic assays do not perform well in cases of acute enteroviral infections and have little use in cases of chronic EV illnesses (Nasri et al. 2007).

Serotyping mostly has no bearing on how a patient is managed. The establishment of EV immunoassays has been impeded by the lack of a broadly shared antigen. Although findings of monoclonal antibodies which cross-react with several EV serotypes are encouraging, additional research is necessary to discover whether

those findings have any clinical significance (Ye et al. 2013). Simply put, serology-based assays are reserved for specialized or public health research lab facilities and only used for specific indications, such as enterovirus serotyping (Peaper and Landry 2014).

The most frequently used techniques for identifying antibodies to enteroviruses are microneutralization assays. In between acute and convalescent periods of enteroviral disease, a serological investigation may show a rise in the level of antibodies that neutralize enteroviruses. In these circumstances, serum samples from both acute as well as convalescent cases must be taken with a spacing of not less than 4 weeks apart. A fourfold or larger rise of antibody titre levels between acute and convalescent samples can be used to retroactively diagnose an acute EV infection. Initially in the course of illness, serum IgM antibodies to CV-B groups can frequently be found, but positive results are not serotype-specific. Antibody titres of 1: 160–320 or higher can indicate recent infections. Nonetheless, serologic diagnosis is time-consuming and is usually impracticable in the clinical context since it requires collecting samples of both acute and convalescent time frames (Chia 2018; Sandoni et al. 2022).

Commercial lab facilities provide type-specific immunoassays which measure antibodies for only some enterovirus serotypes; however, due to cross reactivity and subpar standards, these tests are seldom useful.

Acute enteroviral illnesses really aren't confirmed using serological techniques like neutralization assays or enzyme-linked immunosorbent assays (ELISA). Although there are immunoglobulin M and G assays for the identification of enteroviral infections, their clinical value is constrained due to antigen cross-reactivity between different serotypes (Anwar 2022).

Serological tests can take 2 weeks to complete, rendering sluggish diagnosis and clinical irrelevance. As direct sample isn't really possible in the diagnosis of EV cardiomyopathy, myocarditis, or pericarditis, serological testing may be implicated. As a result, antibody detection may be helpful in these cases. It is possible to measure neutralizing antibodies by testing them against certain enteroviruses (Anwar 2022).

The multiplicity of serotypes of enteroviruses hinders serologic methods. Consequently, it is challenging to distinguish enteroviral neuro-illness from bacterial meningitis with just these methods. As a result, unnecessary tests and interventions involving empirical IV antibiotics are performed often, and hospital stays are prolonged (DeBiasi and Tyler 2004).

6.3.3.6 Viral Culture

Based upon the affected site, EV may be isolated from blood, CSF, or stool. Yield increases if sampling is done from multiple sites. The VP1 gene sequencing approach or neutralizing assays (CDC approved ones) utilizing type-specific antisera may be employed to further determine serotypes of EVs recovered by this method (Chia 2018). Both viral culture as well as shell vial culture require considerable time to conduct, are relatively insensitive and are unreliable since they depend on the existence of viable enterovirus.

Viral cultures are unable to accurately define several EV strains due to improperly collected, handled, or processed specimens, or because the cell lines being employed may be inherently insensitive. When the EV is present at low titres in samples such as cerebrospinal fluid, viral culture might take as long as 8 days for cytopathic effect (CPE) to manifest, and several coxsackievirus-A types will not thrive in cell culture. Also, even though the culture time for shell vial culture with monoclonal antibodies has been shortened compared to tube culture, it is less sensitive than traditional culture (Ye et al. 2013). Neutralizing antibodies, relatively low viral loads at time of diagnosis and the fact that some enterovirus serotypes are inherently uncultivable are all likely to play a role in the viral culture's insensitivity. In most cases, as much as 8 days are needed for the tissue culture method for enterovirus isolation from cerebrospinal fluid. The labour-intensive process of EV culture necessitates cultivation on numerous cell lines. Although extended excretion (4 and 16 weeks, respectively) from both sites can occur after enteroviral disease, faeces sample or throat swab cultures give only circumstantial proof of aetiology in the presence of meningitis or encephalitis (DeBiasi and Tyler 2004). Whereas a CPE normally takes 3–8 days to develop in a cerebrospinal fluid EV culture, PCR data are available within 24 h (~5 h), reducing the turnaround time compared to viral culture in all cases. Hence, polymerase chain reaction tests are preferred since the expenses are comparable (Ye et al. 2013).

6.3.4 Imaging

Patients with enterovirus infection usually present with picture of rhombencephalitis. The spinal and cranial nerves involvement is common. Imaging findings are variable based on patient's symptoms. Imaging can be normal even in positive CSF analysis. Here are the most commonly reported imaging findings in this group of patients.

Computed Tomography (CT)—Fast and feasible specially in emergency department, it is helps in patient's screening and to exclude other mimickers like acute infarction, haemorrhage, hydrocephalus, brain herniation, and tumours. CT scan can be normal in most of cases. If there is a large parenchymal involvement by encephalitis, this can appear as an area of hypodensity at the affected brain. MRI is the second step used for confirming findings and disease characterization.

MRI Brain—The commonest MRI findings are rhombencephalitis; it commonly appears as a hyperintensities on fluid-attenuated inversion recovery images (FLAIR) (Fig. 6.2) and T2-weighted images, involving posterior aspect of brainstem, along with dentate or cerebellar regions. MRI may show normal findings in some patients. Cranial nerve palsies commonly are associated with specific coxsackievirus and adenovirus receptors (CAR) in the cochlea, which are linked with viral docking, seen as abnormal enhancement of the affected cranial nerve (Excoffon et al. 2006; Venail et al. 2007; Wagner et al. 2021). Rare locations that have been reported are the hippocampus, thalamus, putamen, cerebral region along with subcortical region, and

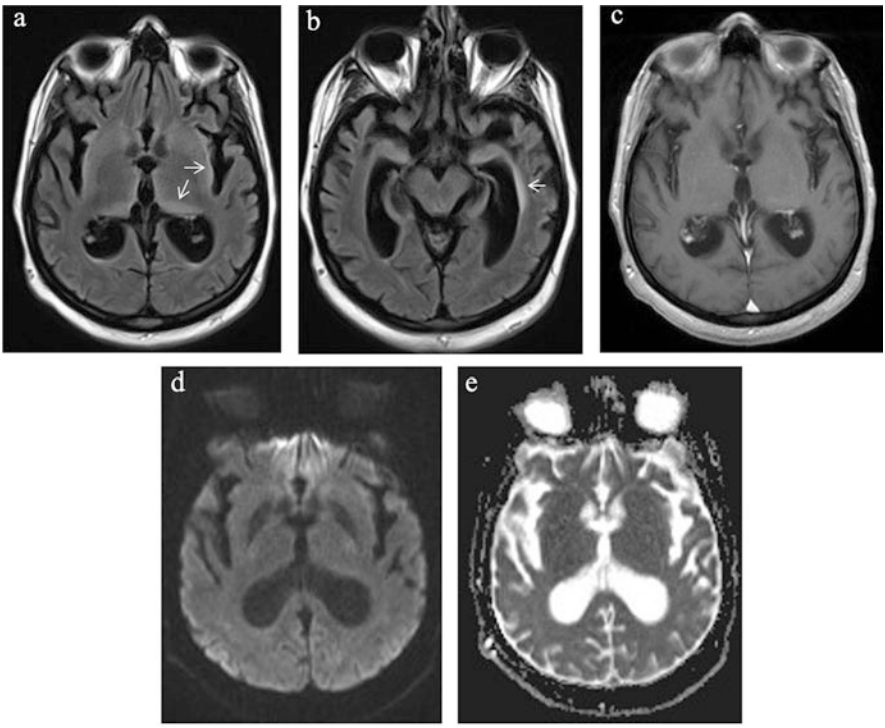

Fig. 6.2 (**a**, **b**) Axial FLAIR images show an abnormal hyperintensities at bilateral Pulvinar, insular ribbon (**a**) and left periventricular WM (**b**) (white arrows), no corresponding enhancement (**c**), or diffusion restriction (**d**, **e**). *Image Source: Courtesy of King Abdulaziz Medical City- Western Region, Jeddah, KSA [Copyright Restrictions – NONE; this image is free of any copyright restrictions]*

corpus callosum in patients with EV71 infection (Jang et al. 2012; Lian et al. 2012; Zeng et al. 2012).

MRI Spine—Patients with spinal involvement usually had acute flaccid paralysis, which appears in MRI as an ipsilateral anterior horn signal changes with or without enhancement. It usually affects lower cervical/upper thoracic cord, or cauda equina nerve roots based on level of involvement. It can be unilateral or bilateral (Chen et al. 2001; Chonmaitree et al. 1981; Chumakov et al. 1979; Kornreich et al. 1996; Melnick 1984).

Electroencephalography (EEG)—Most of viral infections show a picture of encephalitis in EEG. It remains challenging to find a specific pattern of encephalitis in EEG (Rubiños and Godoy 2020). Electroencephalography may demonstrate periodic discharges (unilateral/bilateral), electrical discharges, and generalized slow waves (generalized or focal), which are able to show a non-specific characteristics pattern (Halperin 2017; Rubiños and Godoy 2020; Sutter et al.

2015). The associated neurological changes are mostly regional in nature and less commonly associated with global brain involvement.

6.4 Management and Treatment

6.4.1 General

Most enteroviral infections are self-limiting, requiring only supportive care, with the exception of enteroviral encephalitis, meningitis, myocarditis, neonatal infections, and infections in B-cell deficient patients. Every acute encephalitis case necessitates hospitalization with access to intensive therapy unit, and mechanical ventilation should be prompt, depending on the severity of symptoms. Strict monitoring of the patient's fluids, a stringent lookout for any warning signs of deep vein thrombosis or aspiration pneumonia along with their prevention, medical management of increased intracranial pressure, and any secondary bacterial infections, are all part of the management strategy. Antiepileptics are indicated if the patient develops seizures. Secondary complications including cerebral infarction, cerebral venous thrombosis, SIADH, aspiration pneumonia, and disseminated intravascular coagulopathy are frequent and contribute significantly to morbidity and mortality.

Impending uncal herniation or elevated intracranial pressure in encephalitis that is unresponsive to medicinal therapy (steroid and mannitol) are indications for surgical decompression (Steiner et al. 2005).

6.4.2 Antivirals

There is currently no approved antiviral medication available for the treatment of severe enteroviral infections, including encephalitis and meningitis. Pleconaril, an antiviral that prevents enteroviral replication, was developed as a result of the molecular characterization of enteroviruses. By binding to the viral protein capsid, it prevents enteroviral attachment and uncoating. At doses of 0.1 μg/mL or less, it has wide antiviral effects on enteroviruses, with antiviral effectiveness against more than 90% of the frequently circulating serotypes (Sawyer 2002), although it is currently not licensed for use.

6.4.3 Newer Agents

Owing to a lack of specific enteroviral agents in our repertoire, intravenous immunoglobulins (IVIG) are frequently utilized as a therapeutic as well as prophylactic measure in enteroviral encephalitis. Immunodeficient patients consistently have better outcomes with IVIG, as shown by the encouraging response of intraventricular or intravenous administration of IVIG in patients with X-linked hypogammaglobinaemia (Dwyer and Erlendsson 1988; McKinney et al. 1987).

Enteroviral encephalitis in patients with iatrogenic hypogammaglobinaemia, as seen in patients subjected to rituximab therapy, which is a B-cell depleting therapy, has also been associated with a positive response to IVIG administration; however, its use in patients who are immunocompetent is currently debatable (Schilthuizen et al. 2010; Wagner et al. 2021). Patients with para-infectious enteroviral encephalitis are good candidates for immunomodulatory therapy including corticosteroids and IVIG (Pillai et al. 2015).

6.4.4 Complications/Prognosis

Patients with enteroviral encephalitis, especially adults, are seen to less frequently have severe disease and have better outcomes as compared to other causes of viral encephalitis. These patients also have a shorter length of hospital stay and less severe morbidity; however, there are differences in outcomes based on the infective serotype (Fowlkes et al. 2008).

While a majority of enteroviral infections behave like acute febrile illness with a short-lived course and their natural history is specific for conclusion with either recovery or acute worsening, recent data have also uncovered the presence of persistent infection, as well as an association with lifelong disorders like amyotrophic lateral sclerosis, schizophrenia, type 1 diabetes mellitus, and post-viral cardiomyopathy (Chen et al. 2020). Enteroviral encephalitis in children has also been linked to autism spectrum disorder and attention deficit hyperactivity disorder (ADHD) (Chou et al. 2015; Marques et al. 2014). EV-A71 encephalitis has been associated with long-term sequelae like limb weakness and atrophy, as well as long-term behavioural issues in children (Huang et al. 1999).

Patients with X-linked agammaglobulinemia are prone to develop chronic enteroviral meningoencephalitis of agammaglobulinemia (CEMA), marked by prolonged enteroviral encephalitis. It is characterized by diverse neurologic manifestations with subsequent involvement of multiple organ systems, most commonly associated with echoviruses, and has a guarded prognosis with regards to morbidity and mortality (McKinney et al. 1987).

6.4.5 Prevention

In response to the extensive EV-A71 outbreaks that have been detected in the Far East, a phase III research for an EV-A71 vaccine recently concluded successfully against EV-A71-associated hand, foot, and mouth disease, with up to 90% or more efficacy outcomes observed. (Li et al. 2014; Zhu et al. 2013, 2014). Further efficacy outcomes remain to be seen.

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