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Review Article

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Enterovirus and Parechovirus meningitis in children: a review of the epidemiology, diagnostic challenges, and significance of on-site CSF virology tests in tropical paediatric patients' care

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Abstract:

Enteroviruses and Parechoviruses are increasingly recognized as the cause of aseptic meningitis, especially in the paediatric age group. However, because of indistinguishable clinical features with bacterial meningitis, many clinicians cannot make a clear distinction in disease presentation, and a large number of cases go undiagnosed. Although polymerase chain reaction is the current standard diagnostic approach, it takes many hours or days to get a result and these tests are not available at primary and secondary levels of care in many resource-poor countries. Furthermore, diagnosis is often difficult in children due to nonspecific cellular and biochemical cerebrospinal fluid findings. Some affected children may develop neurologic or/and systemic complications, resulting in prolonged hospital admission, increasing the risk of avoidable deaths, and healthcare expenditures. This review focuses on epidemiology, presentation, and diagnosis of Enterovirus and Parechovirus meningitis, highlighting the challenges in diagnosis and the potential roles of on-site CSF virology tests in improving the quality of paediatric patient's care. The information provided should help early case detection, thereby ensuring avoidance of unnecessary antibiotics, minimal complications, a short period of hospital stays, and a reduction in healthcare-associated costs.

Keywords: Aseptic meningitis; Enterovirus; Parechovirus; Diagnostic challenge; On-site virology test; Children

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Méningite à Entérovirus et Parechovirus chez les enfants: un examen de l'épidémiologie, des défis diagnostiques et de l'importance du tests virologique sur site du LCR dans les soins aux patients pédiatriques tropicaux

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Abstrait:

Les entérovirus et les parechovirus sont de plus en plus reconnus comme la cause de la méningite aseptique, en particulier dans le groupe d'âge pédiatrique. Cependant, en raison des caractéristiques cliniques indiscernables de la méningite bactérienne, de nombreux cliniciens ne peuvent pas faire une distinction claire dans la présentation de la maladie, et un grand nombre de cas ne sont pas diagnostiqués. Bien que la réaction en chaîne par polymérase

soit l'approche diagnostique standard actuelle, il faut plusieurs heures ou jours pour obtenir un résultat et ces tests ne sont pas disponibles aux niveaux de soins primaires et secondaires dans de nombreux pays pauvres en ressources. En outre, le diagnostic est souvent difficile chez les enfants en raison de découvertes non spécifiques du liquide céphalo-rachidien cellulaire et biochimique. Certains enfants atteints peuvent développer des complications neurologiques ou systémiques, entraînant une hospitalisation prolongée, augmentant le risque de décès évitables et les dépenses de santé. Cette revue se concentre sur l'épidémiologie, la présentation et le diagnostic de la méningite à entérovirus et parechovirus, mettant en évidence les défis du diagnostic et les rôles potentiels des tests virologiques sur place dans le LCR dans l'amélioration de la qualité des soins aux patients pédiatriques. Les informations fournies devraient contribuer à la détection précoce des cas, garantissant ainsi d'éviter les antibiotiques inutiles, des complications minimales, une courte période d'hospitalisation et une réduction des coûts associés aux soins de santé.

Mots clés: méningite aseptique; Entérovirus; Parechovirus; Défi diagnostique; Test de virologie sur place; Enfants

Introduction:

Despite advances in antimicrobials, infections of the central nervous system (CNS) remain a major cause of many life-threatening disease conditions, with aseptic meningitis at the forefront, especially in the paediatric age group. Aseptic meningitis (AM) is an acute inflammation of meninges of the brain and spinal cord in which the cerebrospinal fluid (CSF) is negative for bacteria (1). AM is specifically caused by Enteroviruses (EVs) and Parechoviruses (PeVs), however, viruses such as Herpes simplex virus types I & II (HSV I & II), Varicella zoster virus (VZV), Adenovirus (ADV), Rhinovirus (RHV), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Mumps virus, Human herpesvirus 6 (HHV 6) and HIV have been implicated (2-11). Also, there are non-viral causes such as drugs (12-14), parasites, fungi, and inflammatory diseases (7-9). EBV and Cryptococcus are recovered mostly in immunocompromised individuals (9).

EVs and PeVs are emerging pathogens that constitute two important genera (Enterovirus and Parechovirus) of the *Picornaviridae* family. The family of picornaviruses consists small ($\approx 30\text{nm}$), non-enveloped viruses containing single-stranded, linear, positive-sense RNA, with several important human and animal pathogens including Polio viruses (15,16). Enterovirus genus consists of 15 species [EV: (A-L) and *Rhinovirus* (RV: A-C)], and over 100 serotypes have been described (17,18). The genus Parechovirus contains four species; Parechovirus A, formally Human Parechovirus (HPeV), Parechovirus B (formerly Ljungan virus infecting rodents), Parechovirus C (Sebokele virus), and Parechovirus D (Ferret Parechovirus). Nineteen different genotypes of PeV-A have so far been described and their count is still on the increase (16,19-21).

Because of their pathogenic potential, increasing frequency of detection (even among healthy individuals), and the ability to cause severe infections, EVs and PeVs attracted more attention and became relevant globally (19-

27). But, without clear distinction in clinical presentation and non-specific CSF findings, diagnosis of AM is rarely considered, and only when the first line of care (usually antibiotic therapy) fails (28-32). The situation is worsening in countries with poor laboratory diagnostic services and inadequate intensive care facilities.

The on-site CSF virology tests eliminate the technicalities of sample preparation and processing and produce results in a matter of minutes. They offer a superior advantage in patients' management through early recognition of cases and exclusion of other suspected pathogens. Reduction in the use of unnecessary antibiotics, expendable costly investigations, as well as guiding investigations and follow-up for potential complications in severely affected children are among added benefits (29,31,33). In this review, we provided a summary of current knowledge on Enterovirus and Parechovirus meningitis, with emphasis on the paediatric age group.

Methodology:

This article is a narrative review of Enterovirus and Parechovirus meningitis available in the literature. Original and review articles published in English Language were searched for on PubMed, Embase, Scopus, and Google Scholar. Articles reporting information relating to the biology and classification of Enterovirus and Parechovirus, epidemiology, clinical presentations, and laboratory diagnosis of meningitis caused by these viruses, as well as the diagnostic challenges, and the potential roles of on-site CSF virology tests were retrieved and reviewed.

Epidemiology of Enteroviruses and Parechoviruses

Human EVs and PeV-A are ubiquitous, transmitted mainly by direct contact with respiratory secretions, droplets, nasal discharge, sputum, saliva, or faeces, from symptomatic or asymptomatic carriers, within a family, in

schools, hostels, and chronic care facilities (34-39). Nosocomial (40,41), and transplacental transmission (24,42) have been reported. They cause several diseases in humans (sporadic and endemic) and have the potential for pandemic spread (25,43,44). However, the exact disease incidence is not known. Reports vary by country, demographic characteristics, and virus genotype. EVs typically infects older children and adults while the PeVs predominate in neonates and infants (20,21,31,38,45-52). A pooled-data from Japan, Hong Kong, Denmark, Finland, Netherlands, the USA, and Malawi revealed a prevalence of $\approx 2\%$ for PeV-A in children with suspected viral infections (35,44,52). In under-developed nations, data are limited because the diagnostic facilities are difficult to operationalize and only restricted to

referral laboratories. In tropical Africa, reliable data are only available in countries with good research-link (9,18,19,30,36,39,52-59).

From a recent study in the UK and the Republic of Ireland, the incidence of EV-PeV meningitis was twice that of bacterial meningitis (24). AM is more prevalent during the hot season, usually May to September (10,24,60-63), but can occur all-year-round (10,49,56,63-67). Cases are seen mostly in children less than five years of age (50,63), more males affected than females, and there may be variation in the distribution (30,55,62,63,65). The infection accounts for many admissions into intensive care units, with associated mortality (11,24,29,49,61,68-70). The summary of the detection rates from various countries is shown in Table 1.

Table 1: Detection rates of Enterovirus (EV) and Parechovirus (PeV) in children with suspected meningitis from various countries

Country	Place of study (province/state/city)	Study period	Targeted age (Mean/Median)	Prevalence (%)		Most affected age (Median)	Reference
				EV	PeV		
Australia	Western Australia	Feb-Jul 1992	< 15 years	80/104 (76.9)		< 5 years	(28)
Brazil	São Joaquim da Barra	Dec 1998-Dec 2003	2-6 years	64/294 (21.8)		1-4 years	(64)
	São Paulo	Feb-May 2004	4.5 years	12/23 (52.2)			(118)
Canada	São Paulo	2008-2009	≤ 5 years	49/344 (14.2)			(4)
	Alberta, Manitoba, ¥	Jan 1998-Dec 1999	< 1 to 18 years	233/802 (29.1)			(119)
China	Yunnan	2009-2010	3-14 years	85/524 (16.2)		< 14	(76)
	Luoding, Guangdong	May-Jun 2012	6 years	75/121 (62)		3-5 years	(74)
	Shandong	2014		209/927 (22.5)			(63)
Denmark	Zhejiang	2002 to 2015		206/1757 (11.7)			(120)
	Hebei	Jan-Sept 2015	7 months-16 years	89/268 (33.2)			(10)
Egypt	Cairo	2009-2012	< 5 years		30/32 (94)	39 days	(47)
France	Clermont-Ferrand	Jun 2010-May 2012	1.5 months-12 years		56/100 (56)	< 2 years	(30)
	Clermont-Ferrand	Jan 2008-Dec 2009	2-16 years	17/27 (63)		32 days-2 years	(121)
Germany	Clermont-Ferrand	Jun 2015-Oct 2015	≤ 28 days-16 years	222/246 (90.2)		2-16 years	(77)
	Bonn	Jun 2016-Oct 2016					
Greece	Hannover, €	May 1998-Oct 2008	8 days-17 years	14/327 (4.3)	2/327 (0.6)	< 3 months	(6)
	Athens metropolitan	2008	0-18 years	100/157 (63.7)		6.8 \pm 3.8 years	(71)
Iran	Thessaloniki, £	2013		96/106 (90.6)		7.1 \pm 4.1 years	
	Athens	Jan 1994-Dec 2002	1 month-14 years	47/96 (49)		6-12 years	(93)
	Nemazi, Dastgheib Mashhad city	Mar 2003-Apr 2005	21 days-14 years	14/32 (43.8)		7.73 years	(82)
Italy	Shiraz	2007	0-15 years	105/177 (59.3)		5.2-7.5 years	(83)
	Tehran	May 2001-May 2002	2 months-15 years	13/102 (12.7)		8 month-12 year	(122)
	Tehran	Mar-Sept. 2007	< 1-month -17 years	21/58 (36.2)		5.7 years	(70)
	Tehran	May 2007-Apr 2008	2 months-15 years	13/65 (20)		1-5 years	(3)
Japan	Tehran	2007-2012	< 8 years	275/366 (75.1)	154/366 (42)	20.17m: > 1year	(84)
	Tehran	2009-2011	< 8 years	24/115 (20.87)	51/115 (44)	20.12m: 26.67m	(92)
Netherlands	Northern Iran	Jun 2014: Mar 2015	6 months-13 years	9/50 (18)		2-5 years	(123)
	San Matteo, Pavia	Jan 2010-Oct 2013	< 30 days	4/60 (6.7)			(61)
Palestine	Tilburg and Breda	Mar 2008-Aug 2011	0-16 years	75/141 (53.2)	16/141 (11.3)	50 days:34 days	(45, 124)
	West Bank	July 2012- Nov 2015	< 1-10 years	62/324 (19.1)		< 1 year	(88)
Russia	Northern West Bank	Mar-Oct 2017	0-92 months	54/249 (21.7)		0-92 months	(62)
South Africa	West Siberia	2012-2013	1-14 years	70/143 (50)			(86)
South Korea	Mossel Bay, W. Cape	Dec 2015-Jan 2016	< 10 years	43/63 (68.3)		2-4 years	(55)
Tunisia	Chungcheong	Jun-Oct 2008	≤ 16 years	60/140 (42.9)		2 m-13 years	(125)
	Jinju	Feb 2012-Sept. 2013	1-5 years	20/267 (0.7)	9/267 (3.4)	1.4 m:7.8 m	(75)
Turkey	Monastir & Mahdia	Jan 2011-Jan 2013	< 28 days-16 years	14/143 (9.8)		2-16 years	(85)
UK	Ankara	Jun 1999-Dec 2004	< 1-14 years	104/612 (17)		5.6 \pm 3.4year	(2)
	London	2008-2012	< 1 years		30/40 (75)	< 90 days	(31)
USA	Cornwall	2012-2015	≤ 5 years	20/98 (20.4)		< 5 months	(60)
	England	2016	≤ 5 years	27/140 (19.3)	14/140 (10)	< 5 m: < 2 m	
UK & Ireland	Leicester	Feb 2014-Aug 2017	29-102 days	131/163 (80.4)	32/163 (19.6)	< 90 days	(48)
	Wales & North Ireland	Jul 2014-Aug 2015	< 90 days	668/703 (95)	35/703 (5)	< 90 days	(49)
USA	8 Regions	Feb-Sept. 2014	< 2 months-17years	47/639 (2.7)	12/299 (4)	34 days	(24)

¥ = Ontario, Quebec, Scotia, British Columbia; € = Düsseldorf; Erlangen-Nürnberg; Ludwigsburg; Heidelberg; £ = Drama, Patra, Larisa & Bolos

Socio-demographic factors such as age, gender, season, and study design accounted for substantial disparity in disease prevalence, in countries, and regions within the same country, with studies mostly on EVs. Estimates indicated variation in peak age of the infection, but mostly within the first five years of life (≤ 5 years for EVs versus < 3 months for PeVs). It is important to note that symptoms in neonates are subtle and not different from sepsis-like illnesses, which leads to a serious challenge in diagnosis and reporting, suggesting the need for high-quality surveillance to optimize detection, as country-specific estimates are crucial tools to improve diagnostics and therapeutics for these infections.

Prevailing genotypes/serotypes of EVs and PeVs involved in AM and other infections

On specific serotypes, Coxsackievirus B5 (CVB5), Coxsackievirus A9 (CVA9), Echovirus 6, 9, and 30 and CVB3 are the most commonly reported serotypes from AM and other clinical infections (49,55,63,64,71-78). Other serotypes recovered include Echovirus 1, 3, 4, 5, 7, 11, 13-16, 18, 20, 25, 27, 32 and 33; CVB1, CVB2, CVB4, CVB6; CVA2, CVA4-6, CVA10, CVA15, CVA16, CVA21 and EV71 (6, 10,28,45,49,55,56,60-67,71-73,75,76,79-89). On the other hand, PeV-A3 is the mostly recovered genotype (31,47-50,60,90,91) while other genotypes recovered are PeV-A 2 and 1 (47,92).

Clinical presentations of meningitis caused by EVs and PeVs and complications

Usually, there is no clear distinction in clinical presentations of meningitis caused by EV, PeV, or bacteria agents. Fever is the most common symptom and is usually moderate to high grade. Nausea, vomiting, diarrhea, poor feeding, irritability, convulsions, headache, and altered level of consciousness are notable symptoms (24,31,56,60-64,71,77,82,93-95). Headache, vomiting, neck rigidity, and lethargy are pronounced in children with EV meningitis (77, 94,96). Patients may present with typical features of upper respiratory tract infections, and maculopapular rashes mostly in those with PeV infections (31,60,97).

The severity and risk of developing complications depend on the virus type, patient age, and the interval between disease onset and presentation to the physician (31, 32,94,98,99). Abnormalities of the white matter and neurodevelopmental delays are the common sequelae (24,31,32,47,50,51,91,98,

100,101). Subdural hemorrhage, coronal infarction, cystic encephalomalacia, periventricular leukomalacia, and ventricular dilatations are specific complications. Such patients may manifest with failure to thrive (FTT), recurrent seizures, visual impairment, and global hypotonia (11,24,31,49,91,102). Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADS) has been reported (70). Shaker and Abdelhamid reported 50% mortality in patients who tested positive for EV (30), while some other studies also reported considerable mortalities (24,31,70).

Laboratory diagnosis of EVs/PeVs infections and challenges

Laboratory testing is essential for the definitive diagnosis of infectious meningitis, particularly in the young infant, because clinical disease presentation lacks predictive value. CSF pleocytosis and elevated protein are the recommended criteria for diagnosis, however, many studies showed varied results (10, 24,28-32,56,60,73,75,88,91). With contradictory reports of other markers such as C-reactive protein (CRP), lactate, mononuclear, or polymorphonuclear cells counts (24,91,103, 104), there could be uncertainty in diagnosis and treatment. Therefore, it should be noted that with the positive signs and symptoms of meningitis, the absence of CSF pleocytosis, elevated protein, or other markers of interest does not rule out EV or PeV meningitis.

The mainstay of the diagnosis is molecular-based assays on appropriately collected samples. Cell culture is one of the most popular methods for virus isolation, evidenced by the cytopathic effect (CPE), which alter specific characteristics of the cells. However, cultures are intensive and some viruses (most especially PeVs) do not replicate in commonly used cell lines. Thus, researchers nowadays are reluctant to use cultures and tend to adopt PCR techniques for relative simplicity and short window for results (21,23). Recently, we evaluated the diagnostic sensitivity of cell culture, real time RT PCR, and nested RT PCR for EVs and PeVs, and real time RT PCR demonstrated the highest sensitivity and negative predictive value (NPV), particularly for EVs (unpublished work). Specifically, real-time PCR is the recommended test for EVs and PeVs in all clinical specimens (21,23). The PCR assay relies on the extraction and purification of nucleic acid, then exponential amplification of the target sequence, using a thermostable polymerase and specific primers.

Unfortunately, most tropical and sub-

tropical countries cannot establish qualitative molecular-based diagnostic tests in basic healthcare settings. This contributes to the enormous burden of ill health as infectious diseases represent the major cause of death in most of the countries. Another fundamental problem is the lack of incorporation of EVs and PeVs among the list of priority infections. This significantly deterred identification of the pathogens even in developed nations. Therefore, misdiagnosis and failure to treat a serious infection or wasting expensive treatment on those not infected remain a serious obstacle. Even without targeted treatment, early identification of infections has economic benefits, which include stopping the use of unnecessary antimicrobial drugs, minimizing expendable investigations, and shortening the length of hospital admissions (24,105,106).

On-site CSF virology tests and management of EV and PeV infections

The WHO has established the ASSURED (Affordable, Sensitive, Specific, User friendly, Rapid, and robust, Equipment-free, and Deliverable to end-users) criteria (107) for diagnostics in a resource-poor setting. This aimed at providing better management of diseases through immediate delivery of results and a rapid record of the disease status, improve clinical decision-making. The cost-effective on-site CSF virology tests employ reverse-transcriptase polymerase chain reaction to rapidly identify the presence of viral RNA in CSF of a suspected infected individual. These offer superior advantages over conventional nested PCR and real-time PCR by providing prompt identification of the pathogen, guide selection of therapy, and minimize complications. Added advantages include short time window for results (rapid turnaround time), antimicrobial stewardship through appropriate prescribing practice, reduction in financial costs, and improve patient outcomes (8,9,108-114). Additionally, the WHO recommended criteria of the physical structure and human resources as key elements of a virology laboratory (115) can be adjusted to suit the desired need in a particular setting, hence, guaranteeing the feasibility of carrying out these tests in most of our local clinics and hospitals.

Currently, there are no antiviral agents licensed for the treatment of EVs and PeVs infections, but vaccines are available only against PVs, and China licensed an EV71 vaccine in December 2015 (116). Researchers are currently exploring the potential benefits of intravenous immunoglobulins (IVIGs), predni-

solone, and other compounds in the management of EVs and PeVs infections. Of recent, a compound 2'-C-methylcytidine, an inhibitor of viral polymerase, demonstrated promising results against PeA-1 and 3 *in-vitro* (117).

Conclusion:

Enteroviruses and Parechoviruses are the leading causes of aseptic meningitis, and there exist indistinguishable presentations with bacterial meningitis, while CSF pleocytosis and biochemical tests show limited roles in diagnosis. The disease prevalence varies in different geographical regions, mainly affected by socio-demographic factors, and E9, 30, 6, 16, CVB5, CVA9, CVB3, and PeV-A3 are commonly isolated virus serotypes. Although the WHO recommends syndromic management in settings with limited access to laboratory diagnostic services, the economic burden of treating common causes of the syndrome is outrageous and merely impossible in local settings. With the evolution of high precision point-of-care CSF virology tests, stockholders should explore their benefits to optimize the quality of care in children with EVs and PeVs meningitis, most especially in resource-poor settings.

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Conflict of interest:

Authors declare no conflict of interest.

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