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Review

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Measles-induced encephalitis

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Summary

Encephalitis is the most frequent neurological complication of measles virus infection. This review examines the pathophysiology of measles infection and the presentations, diagnosis and treatment of the four types of measles-induced encephalitis including primary measles encephalitis, acute post-measles encephalitis, measles inclusion body encephalitis and subacute sclerosing panencephalitis. The early symptoms of encephalitis may be non-specific and can be mistakenly attributed to a systemic infection leading to a delay in diagnosis. This review provides a summary of the symptoms that should cause health care workers to suspect measles-induced encephalitis.

Introduction

In the United Kingdom (UK), the incidence of measles virus infections has gradually increased since 2006. Recent outbreaks in 2013 include in the North West of England where 376 cases were confirmed[1] and Swansea where 664 cases were confirmed over a 9-month period.[2] The increased incidence of measles has meant that its complications such as encephalitis (inflammation and swelling of the brain) are also seen more frequently.

Several reasons have been identified to explain why some clinicians are not adequately aware of measles-induced encephalitis. Common symptoms of encephalitis such as fever and altered level of consciousness are not specific for encephalitis and can be mistakenly attributed to a systemic infection leading to a delay in diagnosis.[3] The relative rarity of encephalitis may also be a reason for clinicians' unfamiliarity with the condition.[4] Although encephalitis is an uncommon complication of measles infection, the fact that outbreaks are still seen and that encephalitis can be difficult to recognize means that clinicians need an increased awareness of the condition. Consequently, in 2012 guidelines were developed to assist management of viral encephalitis.[4]

Measles pathogenesis

Measles is a paramyxovirus constructed of a single negative sense strand of RNA contained within a double-layered envelope. Measles is highly contagious and transferred between humans contained in respiratory aerosolized droplets. The virus initially infects dendritic cells in the alveoli.[5] These cells

drain into nearby lymph nodes and infect lymphocytes leading to viral replication. Infected cells circulate in the blood and spread around the body delivering the virus to organs such as the skin, lung, liver, spleen and brain. After an incubation period of 6–19 days, prodromal symptoms develop, including a stepwise increase in fever to around 39°C or higher, cough, coryza, conjunctivitis and a cluster of white lesions on the buccal mucosa known as Koplik spots that are pathognomonic for measles (Figure 1). Two to four days after the prodrome, a cell-mediated reaction involving T-helper cells releasing interferon α and interleukin-2 leads to the formation of a morbilliform rash characteristically beginning on the face and head and spreading to cover the whole body (Figure 2).[6] The rash remains for 5–6 days and then fades in the order it appeared.

Encephalitis pathogenesis

Encephalitis is an inflammation of the brain parenchyma and typically manifests with a triad of symptoms comprising fever, headache and altered level of consciousness. Other symptoms include disorientation, behavioural and speech disturbances and neurological signs such as hemiparesis and seizures.

Diagnosis

The clinical history should suggest a brain infection to the clinician. The definitive diagnosis is made by brain biopsy, but this is an invasive test. Instead, surrogate markers for brain inflammation are used: for example neuroimaging, such as magnetic resonance imaging (MRI), can show changes consistent with encephalitis. Analysis of cerebrospinal fluid (CSF) following a lumbar puncture often reveals a lymphocytic pleocytosis and increased protein content. In some patients, an electroencephalogram (EEG) may also be helpful.

All patients with encephalitis should have a CSF polymerase chain reaction (PCR) test for HSV1, HSV2, Varicella zoster virus and enteroviruses as these will account for the aetiology of 90% of encephalitis cases.[4] If the aetiology remains unclear, further testing for pathogens should be performed based on the clinical history and in consultation with a specialist in microbiology, virology or infectious diseases. A recent history of measles infection, in the patient or a close contact, should prompt testing to identify measles as the cause. Measles-specific antibodies, in particular immunoglobulins (Ig) G and M, can often be detected in the serum, suggestive of a systemic measles infection, and detection in the CSF indicates an intrathecal antiviral immune response.[7] If an infection is ongoing, measles virus RNA can be detected in the CSF using real-time PCR.[8]

Measles-induced neurological syndromes

Presentations of measles-induced encephalitis include primary measles encephalitis, acute post-measles encephalitis, measles inclusion body

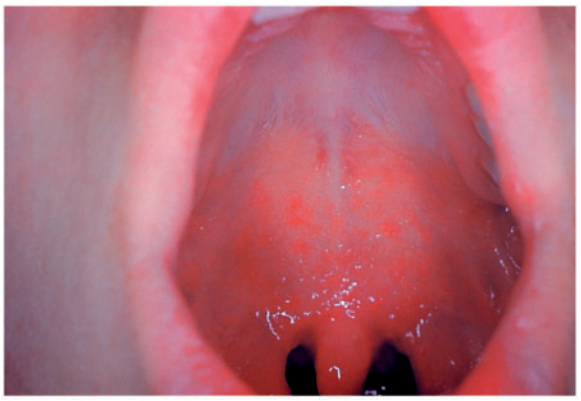

Figure 1. Koplik spots are the small white spots on the pharynx (Reproduced with permission from the CDC).

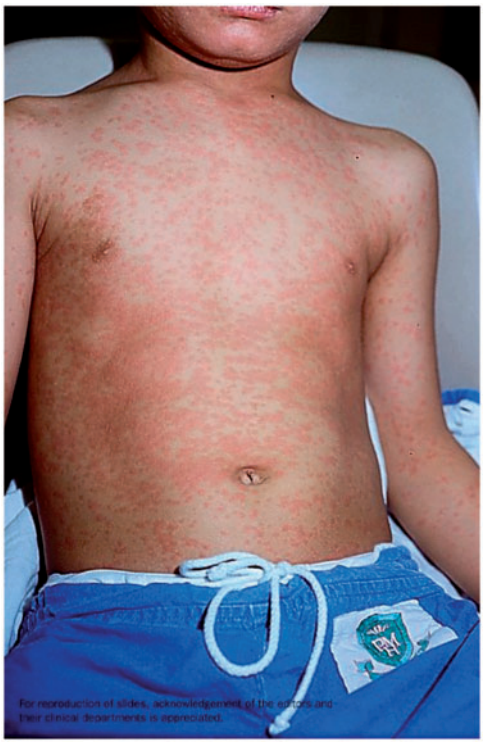

Figure 2. Morbilliform rash (Reproduced with permission from Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong SAR).

encephalitis and subacute sclerosing panencephalitis (SSPE).

Primary measles encephalitis

Encephalitis concurrent with measles infection affects 1–3/1000 patients with measles infection and is referred to as primary measles encephalitis. Typically, the brain becomes infected during the rash phase of the infection. The primary mechanism of infection is unclear, but onset at the early phase suggests a primary viral invasion of neurological cells followed by chemokine induction and lymphocytic infiltration.[9] The detection of measles virus RNA in the CSF lends support to this theory.[10] Treatment is largely supportive. The mortality rate is 10–15% and a further 25% of patients endure permanent neurological damage.[6]

Acute post-measles encephalitis

Encephalitis may also be caused by immune-mediated brain inflammation subsequent to measles infection. The condition is referred to as acute post-measles encephalitis. Approximately 1 in every 1000 children is affected following a measles infection[6] and 1–2/1 000 000 following live measles vaccination.[11] It is the most frequent central nervous system (CNS) complication of measles virus infection[12] and occurs 2–30 days after infection.[13] Because the symptoms can develop soon after measles infection, it can sometimes be difficult to decide whether a patient has primary measles encephalitis or acute post-measles encephalitis. Indeed there may be elements of both acute viral infection, and the inflammatory response occurring in patients, and it may be that there is an overlapping spectrum. In practical terms, if clinicians felt there was extensive brain swelling on imaging they would err towards treating this with steroids (see later).

It has been proposed that acute post-measles encephalitis develops by molecular mimicry.[14] A circulating antibody reacts with a myelin protein, causing CNS dysfunction. As well as the typical symptoms of encephalitis, these patients may also have disturbed vision, difficulty urinating and hyporeflexia. Acute post-measles encephalitis relapses in one-third of patients[15] and sufferers are thought to have a higher risk of developing multiple sclerosis, although the precise increase is unclear.[16]

Treatment

Acute post-measles encephalitis is primarily treated using corticosteroids; intravenous IgG is a possible second-line treatment.[15] Mortality is ~5% in children and 25% in adults.[15] Some children who appear fully recovered demonstrate subtle long-lasting deficits in attention or decision-making ability or behaviour when evaluated more than 3 years after acute post-measles encephalitis.[16]

Measles inclusion body encephalitis

Measles inclusion body encephalitis most commonly occurs in immunodeficient children. The average age of those affected is six and onset is within 1 year of measles infection or vaccination. Typically they suffer from altered mental status, motor deficits and seizures. Measles virus is persistently present and the T-cell mediated hypersensitivity morbilliform rash does not develop or is minimal because of impaired T-cell function. Initially, CSF analysis appears normal, although mild pleocytosis and elevated protein may be observed. Levels of measles-specific antibodies in the CSF rise as the disease progresses. Measles viral RNA can be definitively detected in brain cells following a biopsy.[6] Treatment is supportive although ribavirin may help.[17] Mortality is 75%.[6]

Subacute sclerosing panencephalitis

SSPE affects 1/25 000 measles infections but the incidence is higher among children infected at a younger age. Children infected with measles under 1 year have a risk of ~1/5500.[18] It is thought there is a failure to completely clear the virus following acute infection often in the first 2 years of life and the virus mutates, resulting in persisting and worsening infection.[19] SSPE primarily affects children and symptoms develop 6–15 years after measles infection. Initial symptoms include behavioural changes and cognitive decline. Within weeks or months these symptoms become more obvious and motor dysfunction symptoms develop. Seizures may occur, often myoclonic in nature, and 50% of patients experience ocular disturbances such as necrotizing retinitis. Patients decline into a coma. The changes can be grouped into four stages (Table 1). Death often follows the onset of symptoms within 3 years.[6]

The diagnosis is confirmed by finding very high titres of measles antibody in the CSF. EEG complexes can be visualized during sleep and are bilaterally synchronous with sharp waves lasting 2–3 s, occurring every 2–20 s. MRI scans monitor the progression of the disease. Lesions first appear in the grey matter of the brain. As SSPE progresses they are replaced by lesions in the periventricular white matter. The lesions progress to affect deeper

structures and the brainstem. These structures progressively atrophy.

Treatment

Treatment is symptomatic and supportive, although a range of antiviral regimens has been attempted. One patient treated with intraventricular interferon α, inosiplex and high dose ribavirin improved for 10 months before suddenly deteriorating and dying.[21]

Prevention

Following the introduction of a measles vaccine in 1963, the worldwide number of measles related deaths decreased by 95% by 1995. However, in the last decade of the 20th century outbreaks of measles occurred where people were unvaccinated or had received only one of the two required doses because prior to 1992, only one dose was recommended. In 2010, the World Health Assembly committed to reducing the global number of measles deaths by 95% of the 535 300 deaths seen in 2000 by 2015 with a view to eradicating the virus.[22] A campaign of mass vaccinations reduced the global number of measles deaths to 122 000 in 2012.[23] Africa, Eastern Mediterranean, South East Asia and India are regions still experiencing high numbers of measles deaths and in continued need of campaigns to ensure individuals are given the correct regimen of measles containing vaccine.[23]

In the UK, vaccination coverage for measles fell after a highly publicized article in *The Lancet* linked the measles mumps rubella vaccine (MMR) to autism.[24] Public confidence in the MMR vaccine declined amid concerns it could cause autism. The article was discredited, the lead author struck off by the GMC and no evidence found to support the concerns but the damage to public confidence was done.[25,26] Measles incidence in the UK has gradually risen since then and was again declared endemic in 2008 (Figure 3). In 2012, 2030 cases of measles were confirmed in the UK, 85% more cases than the number diagnosed throughout 2011.[1]

It has been calculated that to eliminate measles in Western countries, herd immunity must be acquired by vaccinating 92–96% of children.[27] In the UK, before the paper linking MMR to autism, uptake of the MMR at 2 years of age was >90%. In 2003, only 80% of toddlers were vaccinated, insufficient to provide herd immunity.[28] A case report described the mortality of two children following encephalitis associated with measles infection.[29] The doctors reporting the case cautioned that in a time of waning national immunity to measles virus, physicians should be particularly aware that measles can cause potentially fatal encephalitis.[29]

In European countries such as Germany, Italy, Romania, and the Netherlands low vaccination coverage has led to recent outbreaks (Figure 4).

Table 1 Clinical stages of SSPE[20]

Stage	Change due to SSPE
Stage I	Behavioral decline (lethargy, inattention or temper-tantrums) and cognitive decline
Stage II	Myoclonic jerks, seizures and dementia
Stage III	Rigidity, extra-pyramidal symptoms, progressive unresponsiveness
Stage IV	Coma, vegetative state, autonomic instability and akinetic mutism

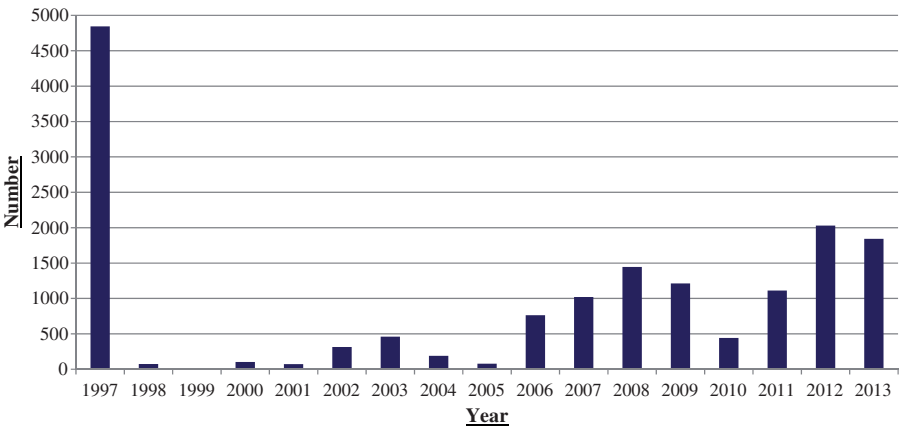

Figure 3. Number of measles cases by country between Jan-Dec 2013 (Reproduced with permission from the ECDC).[30]

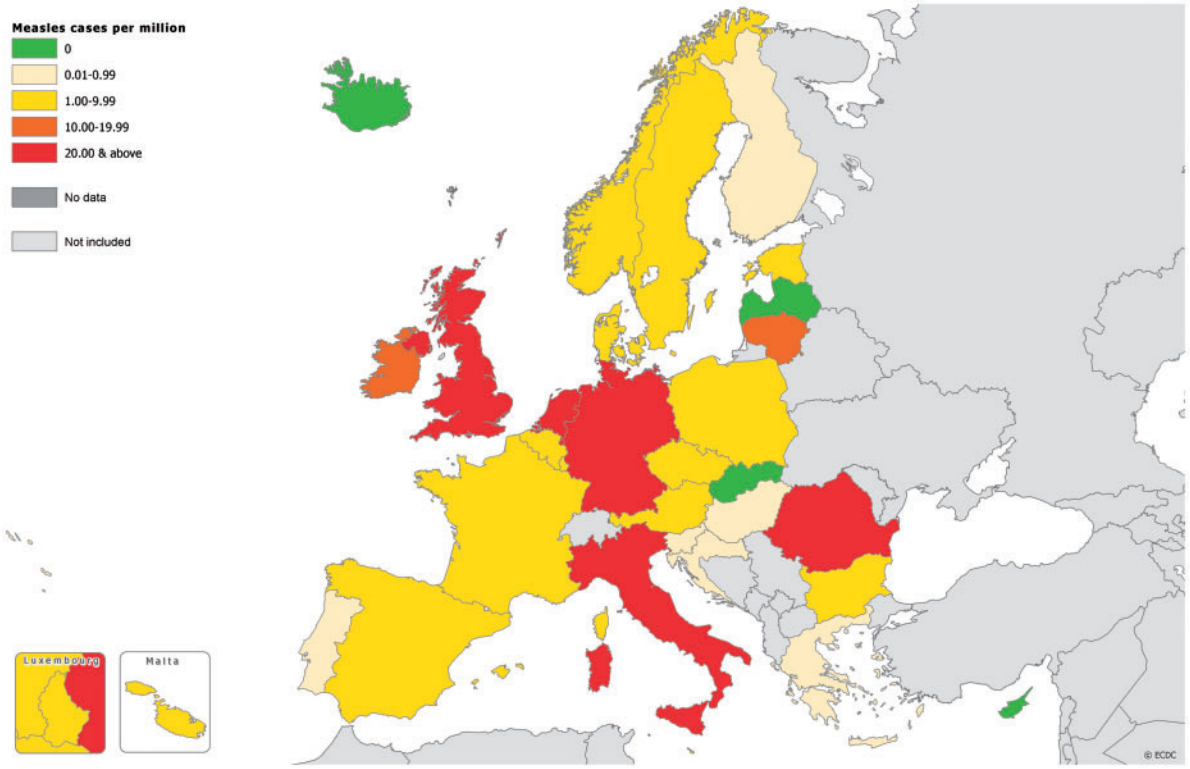

Figure 4. Number of measles cases by country between January and December 2013 (Reprinted with permission from the ECDC).

Table 2 Signs and symptoms of measles-induced encephalitis

Signs and symptoms of measles-induced encephalitis	
Measles symptoms	Encephalitis symptoms
Fever	Fever
Morbilliform rash	Headache
Cough	Altered level of consciousness
Coryza	Behavioral disturbances
Conjunctivitis	Disorientation
Koplik spots	Speech disturbances
	Seizures
	Nausea
	Vomiting
	Hemiparesis

Eight thousand two hundred thirty cases were reported in European countries in 2012 and eight cases were complicated by measles-induced encephalitis.[30] Individuals should be strongly encouraged to become vaccinated against measles if they have no prior immunity before travelling to these countries. Doctors should consider measles and its possible complications as diagnoses for patients who recently travelled to or emigrated from areas of high measles prevalence. It would be prudent to specifically ask about previous measles infections in the medical history.

Conclusion

Almost a decade after the warning from doctors about the consequences of not having herd immunity, measles has been declared endemic in the UK. Encephalitis is a dangerous and destructive ordeal for patients and their families to endure. Medical teams may be unfamiliar with the symptoms leading to delays in diagnosis. As the number of measles infections increases it becomes more likely that complications such as encephalitis develop. Measles-induced encephalitis occurs more frequently in developing countries as a result of poor vaccination coverage leading to epidemics.[31] These conditions have the potential to reappear in developed countries such as the UK if an inadequate number of individuals are vaccinated.[32] It is important that doctors recognize and investigate symptoms that may indicate measles-induced encephalitis (Table 2), particularly if an outbreak of measles is current. The management of suspected encephalitis guidelines published in 2012 recommend that a constellation of symptoms,

including a current or recent febrile illness along with altered behaviour, cognition, personality or consciousness, or new seizures, or new focal neurological signs, should cause the physician to consider an immediate lumbar puncture that could lead to a prompt diagnosis of encephalitis.[4]

Conflict of interest: None declared.

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