International Journal of Research in Medical Sciences
Oza YR et al. Int J Res Med Sci. 2024 Aug;12(8):3129-3133
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20242256

Review Article

Understanding progressive rubella pan encephalitis: a rare neurological disorder

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Received: 26 May 2024
Accepted: 01 July 2024

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ABSTRACT

Progressive rubella panencephalitis (PRP) is a rare late complication of rubella that affects mainly teenagers. It is characterized by progressive white matter destruction, gliosis and cerebral atrophy, similar to subacute sclerosing panencephalitis (SSPE) and congenital rubella syndrome. This paper examines the complexity of PRP, its clinical manifestations, pathogenesis, diagnostic criteria, treatment and prophylaxis. PRP should be considered in adolescents with progressive dementia with pyramidal and cerebral dysfunction. With respect to the most affected children, survival and recovery is expected to be poor, with high mortality rates, especially in the first six months of life. The development of progressive spasticity, ataxia, mental deterioration and convulsions in late childhood and early childhood with mothers' rubella or stigmata histories is the subject of research on PRP. Therefore, continued efforts to understand and address PRP are important to improve the quality of diagnosis, treatment and ultimately the quality of life of affected persons.

Keywords: Rubella, Panencepalitis, SSPE, Congenital rubella syndrome

INTRODUCTION

Rubella, commonly known as German measles, is a viral illness caused by the rubella virus. Although often considered a mild childhood disease, its implications can be far-reaching, especially when contracted during pregnancy. Rubella infection in expectant mothers can lead to congenital rubella syndrome in the fetus, characterized by a range of birth defects including deafness, blindness, heart defects, and intellectual disabilities.[1]

In the postnatal population, while most individuals experience only mild symptoms such as fever and rash, some may develop more severe complications.

One of the rare but devastating complications associated with rubella is progressive rubella panencephalitis (PRP). PRP is a progressive neurological disorder that occurs years after the initial rubella infection. It is believed to result from persistent rubella virus infection of the central nervous system.[2] This chronic infection leads to inflammation and degeneration of brain tissue, causing a decline in cognitive function, motor skills, and overall neurological health.

Understanding PRP is crucial due to its severe impact on affected individuals and their families. As a progressive disease, its onset might be insidious, making early diagnosis challenging. Additionally, there is limited knowledge about effective treatments for PRP, further

emphasizing the importance of research in this area. This article aims to delve into the intricacies of PRP, exploring its clinical manifestations, pathogenesis, diagnostic criteria, and potential therapeutic strategies. By shedding light on this rare complication of rubella, we hope to contribute to better recognition, management, and ultimately prevention of this debilitating condition.

PROGRESSIVE RUBELLA PAN ENCEPHALITIS

PRP is a slow-moving viral infection. It has multiple stages**.** PRP was first reported in 1974, and less than 20 cases have been reported since then. PRP is a rare, late complication of German measles also called rubella infection. It usually occurs years after the initial infection. It affects the central nervous system and can lead to progressive neurological deterioration.[3] The deficits are stable in children with congenital rubella infection; neurologic damage doesn't occur until after the first couple of years of life. We have seen three patients with congenital rubella infection. These patients developed a progressive neurological disease that began in their 20s and was characterized by rigidity, ataxia, cognitive impairment and seizures. Two cases had elevated serum and cerebrospinal fluid (CSF) antibody titers to rubella virus, while all others had high levels of CSF protein and gamma globulin. Several attempts to recover the virus from the brain and body fluids have failed. Progressive subacute panencephalitis was observed in two patients, causing progressive changes to the white matter in their brain.[4] It typically arises following congenital or postnatal rubella infection, often manifesting in the second decade of life. The incidence of encephalitis in rubella is 1 in 6000. Most cases occur during early adolescence and present with symptoms such as dementia and ataxia.[11] A well-documented case involves a 12-year-old boy born to a 19-year-old mother. He had a history of postnatal rubella infection, delayed somatic development, and progressive sensorineural hearing loss. Despite receiving vaccinations against poliomyelitis, rubeola, and vaccinia, his cognitive abilities declined progressively, accompanied by physical growth below the 3rd percentile. Apart from moderate deafness, nystagmus, dysmetria, dysdiadokokinesia, and dysarthria, he exhibited various motor coordination issues, including gait ataxia and myoclonic jerks. His deep tendon reflexes were hyperactive, and he displayed muscle tone abnormalities and occasional choreiform movements.[6] Additionally, there was fine pigment noted in the left peri macular region. PRP should be considered in adolescents with progressive dementia attended by pyramidal and cerebellar dysfunction.[6]

PROGRESSIVE RUBELLA PANENCEPHALITIS IN CONGENITAL CASES

PRP should be considered in adolescents with progressive dementia attended by pyramidal and cerebellar dysfunction. In the congenital form of rubella, virus is transferred across the placenta of the viral pregnant woman. It is particularly during the first trimester of pregnancy that the risk for fetal infection is high. After the eighteenth week the risk of infection of the fetus is reduced. Infection of the fetus during the early period of gestation may develop into a persistent infection and, at birth, the child demonstrates signs of infection.[5,6] The newborn child is highly contagious and may shed virus for months, sometimes for years. Further evidence for a persistent infection are cases of PRP observed in children of 11 to 12 years of age and who are congenitally infected with rubella. The congenital infection may cause embryopathy with retardation of growth and failure in organogenesis. A generalized intrauterine growth retardation is a common feature of congenital rubella. The prognosis for survival and recovery is bad concerning the most damaged children, and the mortality rate is high, particularly during the first 6 months of life.[7,8]

These results show the possible link between rubella virus and progressive panencephalitis.

Pathogenesis of PRP

PRP, a neurological disorder linked to the rubella virus, presents unique pathological features, including widespread destruction of white matter accompanied by perivascular inflammation (Figure 1), gliosis, and significant cerebellar atrophy, similar to subacute sclerosing panencephalitis (SSPE) and congenital rubella.[9] However, in PRP, there's evidence of a subacute encephalitic process characterized by the accumulation of lymphocytes and plasma cells around vessels, along with mild astrocytosis and microglial nodules (Figures 2 and 3), unlike SSPE, which typically shows inclusion bodies. A pneumoencephalogram revealed ventricular dilatation (Figure 4) and an enlarged cisterna magna.[10] Moreover, PRP showcases diffuse and pronounced vascular lesions, indicating degenerative rather than active vasculitis, in contrast to the focal vascular abnormalities observed in congenital rubella, as reported by Rorke and Spiro, Desmond et al, and Singer et al. Townsend et al found similar lesions in infants and teenagers with congenital rubella, albeit with fewer vascular deposits and minimal gliosis in asymptomatic teens.[10] PRP autopsies reveal widespread vascular deposits, suggesting a specific association with the late-onset rubella syndrome, which leads to progressive ataxia and dysarthria due to extensive cerebellar atrophy. The deposits in vessel walls resemble immune complex deposits, implying potential globulin precipitation. Elevated levels of gamma globulins in the CSF indicate IgG production within the CNS, further supported by a high count of perivascular plasma cells. Studies by Meulen et al and Ogawa et al associate persistent viral infections, such as measles in SSPE, with late-onset neurological disorders.[10] SSPE typically manifests diffuse destruction of both white and grey matter while sparing the cerebellum, without vascular deposits, in contrast to the distinct vascular lesions seen in PRP. Neuropathological alterations in PRP, characterized by widespread vascular deposits in white matter and significant cerebellar atrophy (Figure 5), suggest

specificity for the late-onset rubella syndrome, distinguishing it from other CNS disorders, including SSPE.[10]

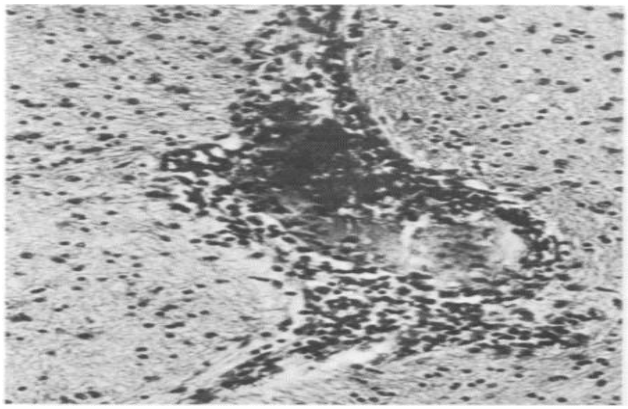

Figure 1: A sample from the hippocampus shows significant accumulation of mononuclear cells surrounding blood vessels and increased astrocyte activity, stained with hematoxylin and eosin, magnification: 220x.

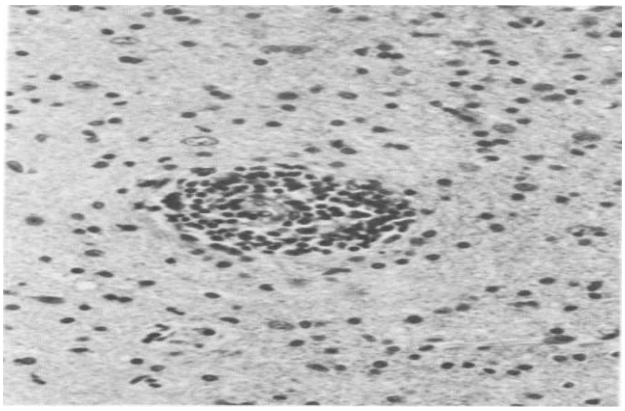

Figure 2: A brain biopsy reveals the presence of lymphocytes and plasma cells surrounding blood vessels in white matter, stained with hematoxylin and eosin, magnification: 300x.

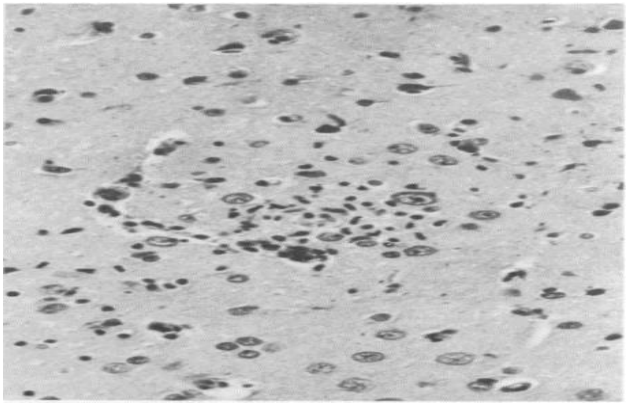

Figure 3: A microglial nodule observed in the cortex of the biopsy sample, stained with hematoxylin and eosin, magnification: 300x.

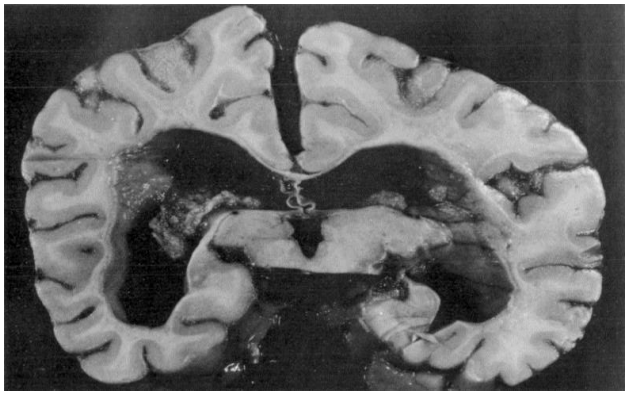

Figure 4: A coronal section of brain at level of splenium showing ventricular dilation.

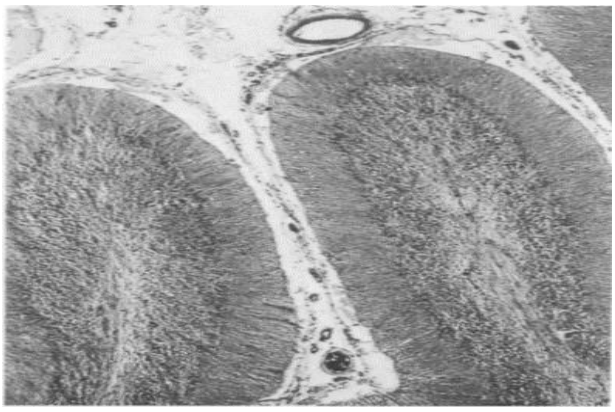

Figure 5: A histological slide of the cerebellar folia illustrates significant atrophy and gliosis across all layers, stained with hematoxylin and eosin, magnification: 50x.

PRP's connection to the rubella virus remains unclear despite the presence of lesions and elevated antibody levels. Unlike SSPE, which is caused by the measles virus, it's challenging to find the rubella virus in PRP brains. Although one study detected virus antigen in CSF cells, evidence of defective rubella virus replication is lacking. In SSPE, high levels of anti-measles virus antibodies and characteristic inclusion bodies in the CSF indicate defective measles virus production.[8] However, in PRP, antibodies against the rubella virus recognize all three structural proteins, suggesting normal replication. The leading theory proposes that PRP originates from a systemic virus infection focusing on the brain, possibly through immune-related mechanisms. Despite limited direct evidence of the rubella virus in PRP brains, the robust immune response suggests its presence. Recent research suggests that the virus might be confined to specific brain cells, such as astrocytes, with new tools offering potential for detection in these cell types. However, the rarity of PRP complicates research into its origins.[5] Defective rubella virus may exist in PRP brains, similar to defective measles virus in SSPE. Unlike measles virus, where individual protein synthesis can be stopped selectively, rubella virus proteins are expressed together,

making antibody production against one protein impossible if any are defective. While some evidence suggests the rubella virus may be present in PRP brains, it's not widespread, suggesting that most pathological changes aren't directly caused by the virus. Instead, immune-mediated mechanisms, such as perivascular infiltration and vascular deposition, appear to drive the pathology. Rubella virus-specific immune complexes in PRP patients' sera may contribute to CNS vascular immunoglobulin deposition, suggesting virus antigen production in the brain. Cell destruction may result from immune-mediated cytolysis of infected cells or an autoimmune response, possibly triggered by molecular mimicry. Notably, a study found a shared antiviral and autoreactive response in cell lines from PRP patients, further supporting this theory.[8]

The magnetic resonance imaging (MRI) results of a 7-year-old girl reveal hyperintense lesions indicative of gliosis, demyelinating lesions, and periventricular calcification, which are frequently observed consequences of rubella infection, as noted by Sawlani et al. Additionally, atrophic changes in the temporal lobe may occur. However, it remains uncertain whether Rubella virus specifically targets the temporal lobe.[9]

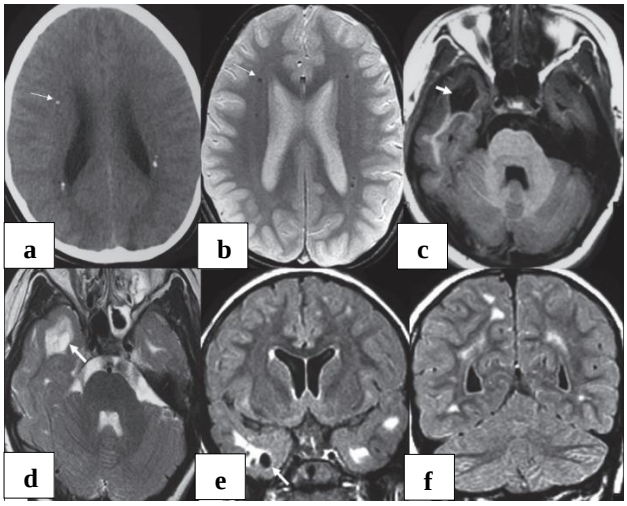

Figure 6: (a) On computed tomography scan; (b) gradient echo axial images, multiple small arrow-headed periventricular calcified nodules are observed; (c) cystic changes in the right temporal lobe (bold arrow) are evident on axial T1-weighted; (d) T2-weighted; (e) coronal fluid-attenuated inversion-recovery images; and (f) additionally, multiple areas of periventricular demyelination or gliosis are visible on coronal fluid-attenuated inversion-recovery images indicating possible consequences of congenital rubella infection.

Diagnosis

The development of progressive spasticity, ataxia, mental deterioration and seizures in a child is considered to be the diagnosis of PRP. It comprises of CSF examination and serologic testing, computed tomography CT, sometimes brain biopsy.[5]

Testing at the minimum involves CSF examination and serologic testing. With an oligoclonal pattern on agarose gel electrophoresis, CSF shows a significant increase in gamma globulin levels, where the normal range of gamma globulin is 3% to 12% of the total protein (15 to 60 mg/100 ml (0.15 to 0.6 g/l)). CSF-serum rubella antibody ratio is also elevated. If there is a history of maternal rubella or stigmata of congenital rubella, PRP should be considered for differential diagnosis of progressive neurologic deterioration occurring in late childhood or early adolescence. In cases of accelerating mental and motor downturn accompanied by prominent cerebellar dysfunction, clinical skepticism should be high.[5]

In the case of cerebellar atrophy and white matter disease, CT may show a ventricular enlargement. Other causes of encephalitis or encephalopathy may need to be excluded by brain biopsy.[5]

Treatment

Symptomatic management is the primary approach for treating PRP since there isn't a specific cure. Symptoms such as seizures, muscle stiffness, and weakness are managed accordingly.[12] PRP could be prevented with more vigilant maternal antepartum care, surveillance, and testing to avoid congenital rubella syndrome. Women of childbearing age in endemic areas should be given a single dose of MMR vaccine. Guidelines must be issued by governments for women trying to get pregnant to test for rubella, immunity status when they consider getting pregnant and must receive MMR vaccine if they are at risk and have no evidence of immunity. Children born to mothers without maternal rubella infection should be administered the first dose of live virus MMR vaccine at 12 months and the second dose through 4 to 6 years of age.[13] Children who are infected with measles virus should be managed in a timely manner symptomatically as there is no specific management. Child must be assessed for any signs of prolonged illness.

CONCLUSION

In conclusion, PRP is a serious complication of rubella, primarily affecting teenagers. Despite diagnostic challenges, including the need for careful clinical assessment and thorough testing, management options are limited to symptom relief. Research into PRP's mechanisms is essential to develop targeted treatments and lessen its impact on patients and families. Continued efforts in understanding and addressing PRP are crucial for improving diagnosis, treatment, and ultimately, outcomes and quality of life for those affected.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Oza YR, Mody M, Avula M, Allahudeen SD, Appana LSM, Ali MA. Understanding progressive rubella pan encephalitis: a rare neurological disorder. Int J Res Med Sci 2024;12:3129-33.