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Microcephaly and Zika Virus: clinical features and associations

Microcefalia e Zika Vírus: características e associações

Microcefalia y Virus Zika: características y asociaciones

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Abstract

Objective: To discuss the association between microcephaly and intrauterine infection by Zika virus. Microcephaly occurs when a child is born with a head smaller than expected when compared to babies of the same sex and age. Known causes of microcephaly include congenital infections. The increase in the number of microcephaly cases in Northeast Brazil between October and November 2015, which coincided with the emergence of Zika virus in the country in May of the same year, led to the hypothesis of an association between microcephaly and intrauterine Zika virus infection. Zika is an arbovirus that is closely related to yellow fever and dengue viruses. *Aedes aegypti* mosquitoes are the primary vector of transmission. Possible transmission through sexual contact and blood transfusion, as well as the implication of other vectors, such as *Aedes albopictus* and even *Culex sp* increases the need for preventive action. The test for viral detection is ideally performed before the 5th day following the onset of symptoms. Serology tests are not yet widely available in Brazil. **Methods:** We performed a narrative literature review. **Conclusion:** The hypothesis of an association between microcephaly and Zika virus is based on reports of spatial/temporal relationship, pattern of neurologic alterations associated with congenital malformations, and findings of viral RNA in amniotic fluid and fetal tissue. Definitive conclusions about the causality can only be reached after further research and availability of laboratory tests. The current evidence strongly supports the association between microcephaly and Zika infection, and all preventive measures must be stimulated.

Keywords:
Microcephaly
Flavivirus
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Resumo

Objetivo: Discutir a associação entre microcefalia e a infecção materna por Zika Vírus. A microcefalia é o tamanho da cabeça menor do que o esperado em comparação com bebês do mesmo sexo e idade. Entre as causas conhecidas, estão as infecções congênitas. O aumento de casos entre outubro e novembro de 2015 no nordeste brasileiro, que coincidiu com a presença da circulação de novo vírus no país, em maio do mesmo ano, criou a hipótese de associação entre a microcefalia e a infecção materna durante a gravidez. O Zika Vírus é um arbovírus similar ao da Febre Amarela e da Dengue, transmitido principalmente através da picada do *Aedes aegypti*. A provável transmissão por relação sexual e transfusão de sangue, além de outros vetores como o *Aedes albopictus* e possivelmente até o pernilongo (*Culex sp*) aumentam a necessidade de cuidados preventivos em relação à infecção. O exame para detecção viral idealmente é realizado até o quinto dia após o início dos sintomas. Sorologias ainda não são amplamente disponíveis no Brasil. **Métodos:** Revisão narrativa da literatura. **Conclusão:** A associação entre casos de microcefalia e o Zika Vírus é embasada nos relatos de relação têmporo-espacial, padrão de alterações neurológicas associado a malformações congênitas, presença do RNA viral no líquido amniótico e nos tecidos de fetos. As respostas definitivas de causalidade serão possíveis após pesquisas e disponibilidade de exames laboratoriais. As evidências até agora apoiam fortemente esta hipótese e todas as medidas preventivas devem ser estimuladas.

Palavras-chave:
Microcefalia
Flavivirus
Aedes
Zika vírus
Gestantes

Resumen

Objetivo: Discutir las asociaciones entre microcefalia e infección materna por Virus Zika. La microcefalia es el tamaño de la cabeza menor de lo esperado en comparación con los bebés del mismo sexo y edad. Entre las causas conocidas están las infecciones congénitas. El aumento de casos entre octubre y noviembre de 2015 en el nordeste de Brasil, que coincidió con la presencia de la nueva circulación del virus en el país en mayo del mismo año, creó la hipótesis de asociación entre la microcefalia y la infección de la madre por Virus Zika durante el embarazo. El virus Zika es un arbovirus similar al dengue y la fiebre amarilla. El virus se transmite a través de la picadura del mosquito *Aedes aegypti*. La probable transmisión por vía sexual y por la transfusión de sangre - además de otros vectores como el *Aedes albopictus* y posiblemente el mosquito *Culex sp* - aumentan la necesidad de atención preventiva contra la infección. El cuadro clínico es benigno, autolimitado, caracterizado por erupción maculopapular asociado con otros síntomas tales como conjuntivitis, artralgia y la inflamación de las articulaciones. El examen para la detección del virus se realiza idealmente por el quinto día después de la aparición de los síntomas. Las pruebas serológicas no están ampliamente disponibles en Brasil. **Métodos:** Revisión de literatura. **Conclusión:** La asociación entre los casos de microcefalia y el virus Zika se basa en informes de patrón de relación temporo-espacial de los trastornos neurológicos asociados con malformaciones congénitas, el ARN viral presente en el líquido amniótico y tejidos de fetos. Las respuestas definitivas de causalidad serán posibles después de la investigación y la disponibilidad de pruebas de laboratorio. Hasta ahora, las evidencias apoyan firmemente esta hipótesis y todas las medidas preventivas deben ser estimuladas.

Palabras clave:
Microcefalia
Flavivirus
Aedes
Virus Zika
Mujeres Embarazadas

Introduction

Microcephaly occurs when a child is born with a head smaller than expected when compared to babies of the same sex and age.[1] It is formally defined as a head circumference, with an occipital-frontal circumference below the 3rd percentile for gestational age, or as a ratio of femur length to head circumference ≥2 standard deviations below the norm. There are different cutoff points and measures to diagnose microcephaly, but most of them are based on sex, age, or gestational age standards measured at birth. Severe microcephaly is defined as a head circumference more than 3 standard deviations below the mean. In the United States, for example, the incidence of severe microcephaly ranges from 2 to 12 per 10,000 live births, with an overall incidence of microcephaly estimated at 3% of all live births.[2]

In practical terms, considering the World Health Organization (WHO) head circumference-for-age charts, male or female infants born at ≥37 weeks of gestational age with head circumference of at least 32 cm are categorized above the 3rd percentile, and thus do not have microcephaly.[3-5] In the case of infants born before 37 weeks of gestational age, the Fenton or InterGrowth references are usually employed. Each of these reference standards has different cutoff points and therefore different sensitivity ad specificity to detect microcephaly. Victora et al.[6] have recommended the use of the InterGrowth reference, shown to have optimal specificity without compromising sensitivity, for surveillance of suspected cases of microcephaly in Brazil.

Newborns with microcephaly may have a variety of associated problems, depending on the severity of the condition. These include seizures, developmental delay, intelectual disability, problems with balance, difficulties feeding and swallowing, hearing loss, and visual impairment.[2]

The known causes of microcephaly include maternal infections during pregnancy, such as rubella, toxoplasmosis, syphilis or cytomegalovirus. Other causes of microcephaly include severe malnutrition or maternal exposure to alcohol, drugs, or chemical agents during pregnancy (Table 1).

Table 1. Known causes of microcephaly.

Genetic	Chromosomal/genetic syndromes or abnormalities, neuroanatomical abnormalities
Exposure to toxins	Alcohol, radiation, cocaine, tobacco, or other teratogens
Infections	Syphilis, rubella, HIV, cytomegalovirus, toxoplasmosis, herpes simplex, and other congenital infections
Metabolic disease	Diabetes, phenylketonuria among others
Nutritional	Malnutrition
Vascular	Anoxia, hypoxia, or ischemia

Source: Telessaude/RS (2015).

The Latin-American Collaborative Study of Congenital Malformations (*Estudo Colaborativo Latino-Americano de Malformações Congênitas*, ECLAMC) is an epidemiologic surveillance program that collects data from maternities in Latin American countries (in some cases uninterruptedly since 1969). ECLAMC keeps track of the frequency of congenital malformations, investigating and monitoring changes so as to draw attention to uncommon peaks, searching for causes and promoting primary prevention.[7] According to ECLAMC, the incidence of severe microcephaly in participating Brazilian hospitals was 4.53 per 10,000 live births in the period between 1982 and 2013. Approximately half of the cases of microcephaly in this period had associated disorders. Among maternal diseases, syphilis, toxoplasmosis, influenza, epilepsy, and diabetes are considered to be risk factors for microcephaly.[7]

In the past years, a progressive increase in the number of microcephaly cases has been recorded by ECLAMC. This increase is justified by improved diagnosis of prenatal malformations, better cases reporting, and by an increase in the number of referrals of problematic pregnancies to participating hospitals - many of which provide specialized care in areas such as fetal medicine, medical genetics, neonatology, or cardiologic/pediatric surgery. Therefore, many patients are referred to these institutions for pre-natal diagnosis. The rate of microcephaly is higher in most Brazilian hospitals as compared to hospitals from other Latin American countries, except Chile, where the situation is similar to Brazil. Coincidentally, Brazil and Chile have the highest rate of cytomegalovirus infection in Latin America.[7]

Based on the frequency of microcephaly cases per participating Brazilian hospital, the overall adjusted rate is 1.42 per 10,000 live births.[7] The rate of microcephaly is not easily estimated; complicating factors include the heterogeneity of the population, the variety of causal factors, the different definitions used, variations in the quality of diagnostic methods, and the role played by some hospitals as referral centers. The current adjusted rate is 1.98 per 10,000 (CI: 1.478-2.265).[7] This figure may be an underestimation for the Brazilian Northeast, since the prevalence of microcephaly is higher in that region.

ECLAMC has also compared phenotypic data of microcephaly cases from the states of Pernambuco and São Paulo available in the Brazilian Live Births Information System (*Sistema de Informação de Nascidos Vivos,* SINASC) until the beginning of December 2015. The following variables were compared: weight,

gestational age, and proportion of associated cases. The aim was to identify a phenotypic trait-linked to a specific type of microcephaly or to an excessive number of reported, but unconfirmed, cases of microcephaly. Among the difficulties hindering an evaluation is the fact that different information is provided in the two states in live birth certificates regarding congenital defects, which would consequently result in different rates of microcephaly associated with differences in information.[7]

In addition, socioeconomic differences may have influenced the quality of prenatal care in the two states, as well as the number of children with microcephaly caused by low birth weight and the number of premature births and prenatal infections. In the state of Pernambuco, 203 cases of microcephaly and 32 cases of microcephaly with an additional associated diagnosis had been recorded until early December 2015. Of these, 25 occurred in October and November. This peak may have been caused by a change in diagnostic criteria. In relation to other associated malformations, full physical examination of all microcephaly patients was recommended for evaluation of arthrogryposis, clubfoot, scoliosis, and genital abnormalities, among others. From the 28 cases with associated malformations, eight presented genital changes.[7] The SINASC database captures about 1% of birth defects in live births, against an expected 3%; thus, active searches will necessarily translate into an increase in the number of cases recorded.

The increase in the number of microcephaly cases in October and November of 2015 coincided with reports of clinical manifestations compatible with Zika virus infection in May of that year, that is, approximately 30 to 35 weeks before the first microcephaly case was reported.

The aim of the present study was to review literature and discuss the evidence regarding the association between microcephaly and Zika virus.

Methods

For the present study, the literature was reviewed by the research of published materials regarding the topic of interest. Data were collected exclusively on-line, in February 2016, in the following databases: Scientific Electronic Library Online (Scielo), Virtual Health Library (LILACS), and PubMed/National Library of Medicine (NLM). Data were collected in two stages.

The first stage involved a search for articles about arboviruses and microcephaly. The following search terms were employed: ((Congenital, Hereditary, and Neonatal Diseases and Abnormalities [MeSH Terms]) OR “Microcephaly”[Mesh]) AND (“Arboviruses”[Mesh] OR “Encephalitis, Arbovirus”[Mesh] OR “Arbovirus Infections”[Mesh] OR “Flavivirus”[Mesh]) OR (“Zika Virus”[Mesh] OR “Zika Virus Infection”[Mesh]). This research strategy produced 243 quotations.

To identify articles about Zika virus and microcephaly, the following research strategy was employed: ((((zika[Text Word]) OR “Zika Virus Infection”[MeSH Terms]) OR “Zika Virus”[MeSH Terms])) AND (((microcephaly[Text Word]) OR ((“Congenital, Hereditary, and Neonatal Diseases and Abnormalities”[MeSH Terms]))) OR Microcephaly[MeSH Terms]). This resulted in 45 quotations.

Following retrieval, the material for analysis was selected based on criteria of recentness, relevance of information sources, scientific originality, and biological plausibility of the association. This step resulted in a set of articles submitted to critical and interpretative analysis by peers, with the necessary impartiality and objectivity, that were related to information and ideas of authors with the aim of the study.

Results and Discussion

Zika virus

Zika is a flavivirus initially identified in 1947 in Uganda, Africa. In the past 10 years, two Zika virus outbreaks have been observed, one on Yap Island, Federated States of Micronesia, and the other in French Polynesia, with a strain belonging to the Asian lineage, the same involved in cases of autochthonous transmission in Brazil.[8] Presence of the virus has been reported in over 40 countries according to the European Center for Disease Prevention and Control (ECDC).[9]

Zika was first reported in Brazil in May 2015. At the end of that year, the presence of Zika virus in South America and an observed increase in the number of microcephaly and Guillain-Barre syndrome cases led to the hypothesis of an association between these events. Finally, in February 2016, WHO declared that the cluster of microcephaly and Guillain-Barre syndrome cases constituted a Public Health Emergency of International Concern (PHEIC).[10] Up until then, Zika fever was considered to be benign, causing no major impairments when compared to the spectrum of viral manifestations in the flavivirus group.

Zika virus, which belongs to the family Flaviviridae, is a single stranded, positive sense RNA virus. The full virus structure is unknown, but it is probably enclosed in a lipid envelope. Zika is phylogenetically related to dengue, yellow fever, and West Nile viruses - and even to the hepatitis C virus. Zika is an arbovirus, that is, transmitted to humans by infected insects. Zika has been isolated from several species of *Aedes*-genus mosquitoes, such as *Aedes aegypti*, *Aedes albopictus*, and others. Vertebrate hosts include humans and monkeys.[11,12]

Aedes mosquito bites are the most important known mode of transmission, with some species playing a role in enzootic maintenance (in the wild). The transmission capacity of *Aedes aegypti* and *Aedes albopictus* is a major public health problem. *Aedes aegypti*, a mosquito measuring less than 1 cm, is globally distributed in tropical and temperate zones. It does not make a buzzing noise and its bite is frequently painless, causing only minor itching or irritation. This anthropophilic mosquito is well adapted to human environments. Males and females rest in households, indicating that they are highly adapted to humans. Females usually lay eggs in clean water and artificial containers.[13]

Sexual transmission has been suggested following development of illness in the female partner of a man who had returned from an endemic area and who had symptoms during a short period. Because local mosquito-borne transmission of Zika virus was not considered possible, the case supports the idea of direct person to person transmission.[2]

The presence of hematospermia and the identification of the viral particle in semen are also evidence of the plausibility of sexual transmission. Other modes of Zika virus transmission - perinatal, blood transfusion, have been described, but the epidemiological impact of these modes of transmission in unknown.[2]

The magnitude of the impact of infection and dissemination of the Zika virus in humans is difficult to evaluate because only 20% of the cases have clinical symptoms. Incubation period is typically 3 to 12 days. Symptoms last from 3 to 7 days. Duration of the viremic period has not been established, but it is believed to be short. In theory, direct detection of the virus would be possible up to 4 to 7 days after the onset of symptoms, even though the material should ideally be examined until the 4th day for direct viral

detection. Differently from most infectious diseases, the presence of immunoglobulin G (IgG) antibodies has been reported approximately one week after the onset of symptoms, whereas immunoglobulin M (IgM) results are negative. Two weeks after the onset of symptoms, viral detection is negative and IgG and IgM antibodies are positive.[13]

Recently reported clinical manifestations include maculopapular rash (sometimes pruritic), low to moderate fever, non-purulent conjunctivitis, arthralgia and periarticular edema, especially of the hands and feet, myalgia and headaches, in addition to other nonspecific signs, such as asthenia, retro-orbital pain, anorexia, vomiting, diarrhea, or abdominal pain. The course of Zika virus infection is benign in most cases. However, the increase in the number of Guillain-Barre syndrome and microcephaly cases possibly associated with congenital infection have prompted joint efforts by many internationally recognized institutions, leading to partnerships for case-control studies and for the development of vaccines and laboratory tests capable of rapid, specific, and economically viable methods of virus detection.

Investigations are still underway to determine the association between microcephaly and Zika virus infection during pregnancy. Factors that may be helpful to clarify this issue probably include the large-scale availability of serologic assays for identification of virus manifestations and follow-up of susceptible pregnant women or of those testing positive or with confirmed infection.

Association between Zika virus and microcephaly

Many factors support a positive link between microcephaly in newborns and Zika virus infection during pregnancy: the time/space association between presence of the virus and the growing number of microcephaly cases, the finding of viral RNA in amniotic fluid of mothers of microcephaly babies and in fetal brain tissue, malformation patterns that are compatible with congenital infection, ocular findings that are similar to those of other congenital infections, and viral neurotropism.[14-16]

The suspected cases of microcephaly possibly associated with Zika virus infection are spatially scattered, suggesting a viral rather than toxic etiology. Environmental agents, such as toxic agents in water, are spatially restricted. The time association suggests a correspondence between the increase in microcephaly cases and the increase in viral circulation, supporting the idea of a link between infection and malformations. The confirmation of microcephaly in the cases reported in the Brazilian Northeast, in higher numbers than expected, may reflect a real increase in the number of microcephaly cases in Brazil.[17]

The presence of viral RNA in amniotic fluid shows that the virus can cross the placenta, suggesting vertical transmission. Also, the presence of viral RNA in brain tissue of fetuses with malformations presumably attributable to Zika virus indicates that the virus is present in affected tissues even in pregnant women with suspected infection and negative laboratory results, which may be explained by PCR positivity limited to the first five symptomatic days and serology tests not being widely available.[17]

The report of two cases with cerebral calcifications and other malformations identified on obstetric ultrasound, suggesting intrauterine infection, along with viral presence in amniotic fluid, indicate a positive association between maternal infection with Zika virus and microcephaly.[14] The central nervous system alterations that are known so far are compatible with other congenital viral infections, with a characteristic pattern that is similar to that of other viruses (including other flaviviruses); together with the presence of the viral particle in amniotic fluid, this provides evidence that the virus crosses the placenta, reaching the fetus.[14]

Histopathologic findings were limited to the brain and included parenchymal calcification, microglial nodules, gliosis, and cell degeneration and necrosis. Serology tests for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV were negative. The placenta also presented calcification and fibrin deposition.[18]

Freitas et al.[16] evaluated the ocular findings in children with presumed microcephaly resulting from intrauterine Zika virus infection. The study shows similarity between the observed ocular changes and those caused by known congenital viral infections.

The comparison of Zika with other *Flaviviridae* family viruses suggests a neurotropic behavior that is also found in other viruses that causing encephalitis. For example, transmission of West Nile virus through blood transfusion and transplacental transmission have been described in association with malformations.[19]

Calvet et al.[17] identified Zika virus in amniotic fluid of two mothers with fetuses with microcephaly and clinical symptoms compatible with Zika infection. Phylogenetic evaluation showed 97-100% identity with the virus. This weakens the hypothesis of viral mutation as an explanation for the increased incidence of microcephaly.[17] The reports of increased brain anomalies following the Zika epidemic in French Polynesia, the similarity between the viral lineages in the two countries, and the absence of data to prove a change in viral genome support the link between microcephaly and congenital Zika virus infection.[20]

Despite these initial observations, new studies must be performed to confirm the causality link between Zika virus and microcephaly. Other infectious causes, such as syphilis, rubella, cytomegalovirus, may be associated with notified cases. In addition, confounding factors of an environmental nature might be present - for example, factors that facilitate vertical transmission. Even considering the temporal association between increased viral circulation and a growth in the number of cases, active research is always translated into increased reporting, since in general there is underreporting. Especially in the Brazilian Northeast, the change in the definition of case during the evaluation process has contributed to the absolute increase in the number of reported cases. A careful evaluation is thus necessary to distinguish true cases from situations of overdiagnosis.

The first 35 cases of microcephaly with head circumference below two standard deviations revealed the following: all the mothers lived in or had traveled to risk areas, 74% had a rash in the first or second trimester of pregnancy, 71% of the infants had severe microcephaly, with head circumference below three standard deviations, 49% had at least one neurologic abnormality, 27 of the 35 children underwent imaging studies, and 100% of these studies showed alterations.[21]

Establishing a characteristic pattern of congenital changes due to Zika virus requires, in the first place, that other known causes be ruled out. In addition, some genetic syndromes may mimic viral infections. Viral infections do not produce pathognomonic defects, which may weaken the argument used to explain the association between Zika virus and microcephaly.[22]

The finding of viral RNA in newborns, in the mother, or in amniotic fluid is not sufficient to confirm causality - that is, it does not prove that congenital infection with Zika virus causes malformations. The presence of viral RNA in amniotic fluid might be explained simply by the rate of viral exposure in a population, considering susceptibility and the estimated rate of microcephaly. Thus, the combination of events may have occurred by chance.

Confirmation of placental transmission, through identification of viral RNA in amniotic fluid, does not alone support an association between Zika virus infection and the appearance of microcephaly with fetal infection. After all, the total number of pregnant women contaminated with Zika virus is unknown, and thus relative risk cannot be calculated, especially considering the benign and asymptomatic viral presentation in adults, which, in many cases, prevents the identification of pregnant women with previous Zika infection. In fact, affected embryos have been identified in asymptomatic women.[21] In cases of West Nile virus infection, congenital transmission is extremely rare, and infection in the peripartum period or during the first days of life is often considered to be more severe.[19]

The analysis of causal associations between two medical conditions is challenging for researchers. In diseases that spread rapidly, the need for fast answers and the limited knowledge regarding clinical manifestations complicate the definition of suspected case. Before serology tests (IgM and IgG) for Zika virus become widely available for prenatal follow-up, the link will remain questionable. Answers are also lacking for other important questions: if the role of Zika in the development of malformations is confirmed, what is the transmission rate?[21]

The growth in the number of cases does not necessarily entail an increase in the incidence of a disease. The growth in the number of cases in a given region depends basically on reporting by health care professionals. Situations that prompt global debate make health care professionals more attentive, which leads to an increase in the absolute number of reported cases. The evaluation of reported cases, comparing the number of true microcephaly cases with the estimated rate, might reveal the real magnitude of the outbreak. Such data are not yet available. However, the present evidence suggests a real increase in the number of microcephaly cases in Brazil.

Final remarks

Definitive answers will be possible when serologic tests are widely available, with follow-up of a cohort of pregnant women, or, initially, with case-control studies that can produce more evidence to strengthen or weaken the causal association. In Brazil, some research is under way. The preliminary report of a cohort of pregnant women with Zika virus in Rio de Janeiro has identified fetuses with central nervous system abnormalities and other severe outcomes, such as fetal death, placental insufficiency, and intrauterine growth restriction.[22] In turn, studies in other countries, even though based on imported cases, can help to exclude confounding factors associated with the environment, especially considering the specific cases of travelers or tourists.

The existence of endemic areas, the ease of travel, and the benign nature of Zika infection in adults demands attention from health authorities to pregnant women or those of reproductive age. According to primary prevention measures proposed by ECLAMC, all pregnant women should undergo prenatal control to ensure a healthy pregnancy, and should avoid all drugs except those that are essential, also avoiding the use of tobacco and smoking environments.

People returning from trips to areas with autochthonous cases of Zika infection deserve special care. Goorhuis et al.[23] have reported five patients with Zika-like symptoms imported from Suriname in the end of 2015. All had exanthema, fever, and positive viral detection confirming the clinical presentation. The

onset of symptoms occurred not more than 4 days after returning from the trip. The probability of sexual transmission, the uncertainty regarding the effect on pregnant women, and the progressive increase in the number of imported cases have been a reason for concern in many countries. Despite the apparent short duration of Zika viraemia, travelers may still contribute to spread the virus. The risk of introducing autochthonous transmission depends on the density of mosquito populations.[24,25]

The link between microcephaly and Zika virus suggests that the recommendations for prevention of arbovirus infection must be intensified for all women of reproductive age, in addition to the usual health measures involving healthy nutrition, physical activity, avoidance of alcohol and tobacco and other drugs. The recommendation to clear stagnant water to prevent breeding, the use of door and window screens, fans and air conditioning, wearing long and loose clothes, and the use of repellent on exposed skin are still the best methods of prevention. The possibility of sexual transmission justifies the recommendation to use condoms as a preventive measure, especially in pregnant women.

Even without definitive proof that Zika virus is the sole cause of the microcephaly outbreak, the evidence available so far strongly supports this hypothesis. All possible public health measures to prevent the infection of women of reproductive age should, therefore, be implemented.

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