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Best practice guidelines

The etiology of lenticulostriate vasculopathy and the role of congenital infections

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ABSTRACT

Lenticulostriate vasculopathy (LSV) refers to increased echogenicity of the penetrating vessels that supply the basal ganglia and segments of the internal capsule seen on cranial ultrasound. Initially identified in infants with congenital infection, LSV has now been associated with a variety of infectious and non-infectious conditions. Although robust epidemiologic studies are lacking, the available evidence does not support broad evaluation for multiple congenital infections when LSV is identified. We propose screening infants with LSV for congenital cytomegalovirus infection and ensuring that prenatal screening included appropriate testing for syphilis, human immunodeficiency virus, and rubella-immune status. Large, prospective observational studies are needed to determine the incidence of LSV and the relative contribution of infectious and non-infectious conditions to LSV in the neonate.

1. Introduction

Lenticulostriate vasculopathy (LSV) refers to the sonographic finding of increased echogenicity of the lenticulostriate vessels, which arise from the middle cerebral arteries and supply the basal ganglia and portions of the internal capsule [1]. LSV was initially identified on sonography in an infant with congenital CMV infection [2]. Within a few years, multiple other infections were associated with LSV, which became virtually synonymous with congenital infection [3]. However, during the last quarter-century LSV has been recognized in a variety of conditions, both infectious and non-infectious (Box 1). LSV is believed to correlate with adverse neurodevelopmental outcome, although whether this is due to the underlying conditions associated with LSV, injury resulting directly from LSV, or a combination of both remains unclear [4]. In this article, we review the literature in detail to examine the evidence for these associations, with an emphasis on mechanisms that might account for their association with LSV. We summarize the infectious etiologies of LSV and offer a recommendation for the evaluation of affected infants.

2. Pathophysiology

Although congenital infections were initially considered as the primary cause of LSV, it is now clear that many other conditions are associated with LSV [5]. These include not only various infectious etiologies (i.e., cytomegalovirus (CMV) [1,5–13], toxoplasmosis [8,11,14], syphilis [1,3,6], rubella [1,6,8,15], rotavirus [7], meningitis [3], and HIV [14,16]), but also several non-infectious etiologies, including asphyxia, hypoxic–ischemic conditions [1,5,11], ischemic brain infarct [17], chromosomal anomalies [1,5,6,9,11,18], fetal alcohol exposure [5], maternal drug abuse [1,5,8,11], congenital anomalies [19], neonatal lupus erythematosus [20,21], maternal diabetes [22], congenital heart disease [11], twin–twin transfusion syndrome [23,24], and congenital hypothyroidism [10]. More recently, it has been suggested LSV may be a transient finding in healthy preterm infants [25]. Since congenital infections and hypoxic–ischemic events are the most common conditions associated with LSV, we will focus primarily on these two conditions.

2.1. Hypoxic–ischemic conditions

The immature brain demonstrates areas of selective vulnerability to various insults, including hypoxia-ischemia [26]. The basal ganglia and thalamus are highly vulnerable to hypoxic–ischemic injury, and such an injury may represent a “common final pathway” in the etiology and development of LSV. The increased vulnerability of the basal ganglia and thalamus in the immature brain may be explained by several factors. First, the arteries that supply the basal ganglia and thalamus are referred to as “perforating arteries” and differ from cortical arteries. Perforating arteries do not have a rich capillary anastomosis and only one or two smooth muscle layers in tunica media [27]. Yoshino et al. [28] observed in adult rats that myogenic responses by perforating arteries are greater than that in cortical arteries (i.e., the vasodilatation during a fall in perfusion pressure is greater in the former.) In the absence of a rich capillary network, this pronounced autoregulatory

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Box 1
Neonatal conditions associated with lenticulostriate vasculopathy.

- Infectious causes
  - Cytomegalovirus
  - Rubella
  - Syphilis
  - Human immunodeficiency virus
  - Toxoplasmosis
  - Varicella
  - Bacterial meningitis
  - Rotavirus
- Non-infectious causes
  - Hypoxic–ishemic encephalopathy
  - Cerebral infarction
  - Trisomy 13
  - Trisomy 21
  - Maternal alcohol use
  - Maternal drug use
  - Maternal autoimmune diseases
  - Maternal diabetes
  - Hypoglycemia
  - Congenital malformations, including heart disease
  - Inborn errors of metabolism
  - Congenital hypothyroidism
  - Twin-to-twin transfusion syndrome
- Unknown/idiopathic
  - Prematurity

response to systemic hypotension may be the only compensatory mechanism to maintain adequate perfusion of the basal ganglia and thalamus. Secondly, studies that evaluated cerebral blood flow (CBF), glucose utilization and neurotransmitters, demonstrated high blood flow rates and increased glucose demand in basal ganglia and thalamus [29,30]. Repeated episodes of hypoxia–asphyxia induced by intermittent cord occlusion disproportionately injure the striatal GABAergic neurons that are abundant in basal ganglia of the fetal sheep brain [31]. These observations suggest that the basal ganglia and thalamus have high metabolic demand and are therefore particularly vulnerable to hypoxic–ischemic injury when the effective autoregulatory responses are disturbed.

The extent of neuronal damage in the developing brain is dependent on the stage of maturation. Rorke et al. [26] described a phenomenon referred to as 'ferrugination' or 'fossilization' of neurons in areas of ischemic injury. In early stages of injury, the cell congeals into a homogenous bright pink structure that is characteristically PAS positive. Later, the cell becomes encrusted with calcium and iron salts [26]. This seems to be similar to the PAS positive basophilic subendothelial deposits described by Teele et al. [6]; perhaps neonates with LSV who did not have positive calcium or iron staining were in the early stages of injury or had mild disease. Rorke et al. [26] also noted that ferrugination commonly occurred in thalamus after hypoxic–ischemic injury.

2.2. Infectious etiologies

The adverse effects of congenital rubella and congenital syphilis on the fetal brain had already been well-described by the time LSV was initially reported in congenital CMV infection. Central nervous system vasculopathy due to congenital syphilis had been described in 1946, and the endothelial injury and subsequent calcification of brain vasculature caused by congenital rubella infection was recognized in the 1960s [32,33]. Unsurprisingly, LSV was soon identified in a variety of other congenital and perinatal infections [6,34]. Both congenital and perinatal infections are capable of causing vasculitis, with intimal inflammation and destruction [32,35]. The smaller deep penetrating vessels seem to be particularly susceptible to infection relative to the larger cerebral arteries, an association that has been particularly well described for group B streptococcal meningitis [36,37]. These damaged or destroyed endothelial cells lead to deposition of granular, basophilic material on histopathology [32]. This material has been characterized as a mix of fibrin and other proteins with mucopolysaccharides. These deposits may account for the pattern of echogenicity seen on cranial ultrasound scans.

2.2.1. Cytomegalovirus

Congenital CMV infection is the most common congenital infection worldwide, affecting between 0.5–1.5% of liveborn infants [38]. Although only 10% of infants with congenital CMV infection are symptomatic at birth, those who are visibly affected may have significant central nervous system insult, including microcephaly, calcifications, ventriculomegaly, lissencephaly, polymicrogyria, and more [39,40]. Congenital CMV has also been associated with LSV in multiple reports [3,6,41,42]. In their retrospective review of 130 children with LSV, Wang et al. [1] demonstrated that congenital CMV infection was the most commonly identified cause. Antiviral therapy with valganciclovir (or ganciclovir if oral therapy is not possible) has been shown to preserve hearing in infants with symptomatic congenital CMV disease that involves the central nervous system [43]. Amir et al. [13] reported 18 infants with congenital CMV infection who had LSV as their only manifestation of central nervous system involvement. Nine infants treated with antiviral therapy had preserved hearing through 8–27 months, while the remaining nine infants who were not treated all had deterioration of their hearing ($P < 0.001$). For this reason, many experts would recommend treatment for infants with congenital CMV infection and isolated LSV even though LSV was not an inclusion criterion for the original ganciclovir trial. It is worth noting that LSV has also been described in preterm infants who acquired CMV infection postnatally through breast milk [44], but there are currently no recommendations for treatment of postnatally-acquired CMV disease.

2.2.2. Other congenital infections

Congenital syphilis and congenital rubella syndrome were both described as causes of LSV in the initial case series by Teele et al. [6] and were initially second only to congenital CMV as infectious causes of LSV [1]. Other congenital infections associated with LSV include human immunodeficiency virus (HIV) infection and congenital toxoplasmosis. Virkola et al. [45] reported LSV as a finding in three infants with proven ($n = 1$) or probable ($n = 2$) congenital toxoplasmosis. Calcified arteriopathy in children and adults with HIV infection was described early in the pandemic [46], but LSV due to perinatal HIV infection was not recognized until the mid-1990s [47].

Unlike congenital CMV infection, these other infectious causes of LSV are comparatively rare in the United States and Europe. Global efforts to improve rubella immunization rates have resulted in a dramatic decrease in congenital rubella syndrome over the past twenty years [48]. Congenital rubella infection is now extremely rare in the developed world; the majority of reported cases are patients arriving from countries with low vaccine coverage [49]. Mother-to-child transmission of HIV has declined to <0.5% of exposed infants when combination antiretroviral therapy [50]. Congenital toxoplasmosis remains a significant cause of morbidity world-wide, but the incidence continues to downtrend in the developed world [51]. However, congenital syphilis is on the rise after a long period of declining incidence [52,53].

2.2.3. Perinatal infections

Descriptions of LSV associated with perinatal (i.e., not congenital) infections are rare. Neonatal meningitis due to Group B *Streptococcus*, *Acinetobacter*, and pneumococcus has been reported [3]. In their large