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Diagnosis of lenticulostriate vasculopathy – past, present and the future

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ABSTRACT

Aim. The paper represents a review of the current state of knowledge regarding lenticulostriate vasculopathy (LSV) in premature and term neonates.

Material and method. There are reviewed the definition, the history of this diagnosis, the epidemiology, the anatomy of the vessels the etiology and the methods of diagnosis.

Results. LSV is defined as the bright hyperechoic blood vessels in the region of the thalamus and basal ganglia. It was first described in 1960. The incidence is 0.3-2% of live births. The etiology is infectious (congenital rubella, cytomegalovirus, toxoplasma, or other chronic intrauterine infections), hypoxic-ischemic, and in many cases idiopathic (without a clear cause). The diagnosis is mainly done by ultrasonography – the are also proposed classification systems based on the number of vessels affected and/or the echogenicity of the vessels involved.

Conclusion. LSV represents a pathology recognized for a long time, in the past, it was considered mainly associated with chronic intrauterine infections, at present, it is more and more seen as a consequence of perinatal hypoxic events. Further large follow-up studies are needed in order to better characterize the etiology and prognosis of this pathologic condition.

Keywords: lenticulostriate vasculopathy, infections, hypoxic-ischemic injuries, preterm neonates, term neonates, ultrasound

DEFINITION

Lenticulostriate vasculopathy (LSV) was described and defined as the bright or hyperechoic blood vessels in the region of the thalamus and basal ganglia, visible on cranial ultrasound examination of a newborn [1]. LSV can be either unilateral or bilateral, with a branching, linear (strip-like), or punctate-shaped pattern [2].

Some studies showed an association with congenital infections, such as cytomegalovirus, rubella, toxoplasmosis, herpes, and syphilis, as well as with some other conditions including chromosomal abnormalities, a wide range of perinatal conditions (perinatal asphyxia, maternal-fetal alcohol syndrome, feto-fetal transfusions) [1,3].

HISTORY

Also known as thalamostriate or mineralizing vasculopathy, LSV was first reported in the 1960s af-

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ter a congenital rubella epidemic in Philadelphia [2]. After that, in 1985 Grant et al. observed the second-born twin with body weight (BW) of 1240 g, with cytomegalovirus (CMV) infection [1].

In the same decade, Teele et al. found 12 previously unreported cases of LSV. Eight of these babies had congenital infections (cytomegalovirus, n ¼ 5; rubella, n ¼ 2; and syphilis, n ¼ 1), but three had trisomy 13 in the absence of apparent infection [4]. All of these children had vascular pathology remarkable for basophilic deposits consistent with mineralization and hypercellularity. Teele et al. were the first to conclude that the focal vasculopathy observed in autopsy specimens accounted for the echogenicity that was seen on the cranial ultrasounds [4].

EPIDEMIOLOGY

The frequency of LSV varies from 0.5-2% in live births or 0.3- 32% depending on the population that is the subject of research in some studies [1].

ANATOMY

Lenticulostriate arteries are branches that usually emerge from the M1 segment of the middle cerebral artery with the latter originating from the internal carotid artery [5-7]. Physiological variants have been detected over time: LSA may start from a common trunk; other founding was represented by the arising of the arteries from the M2 segment; the origin of the LSA (lenticulostriate artery) can be an accessory MCA (middle cerebral artery); the true or the false bifurcation site; M1 terminal trunks; leptomeningeal branches. LSA can arise as well from the A1, A2 or A3 segment of the anterior cerebral artery [5,8-10]. The number of the LSA vary from 2-15 [5,10].

Further classification into medial and lateral striate arteries was suggested taking into consideration the emergence of the LSA and/or recurrent artery of Heubner (RAH). The recurrent artery of Heubner commonly originates from the A2 segment of the anterior cerebral artery - with the latter also branching from the internal carotid artery. Physiologic variants of RAH exist as well, i.e.: emergence from the A1 segment; A2 segment-Anterior communicating artery junction; absence of RAH or supernumerary arteries [5,11,12].

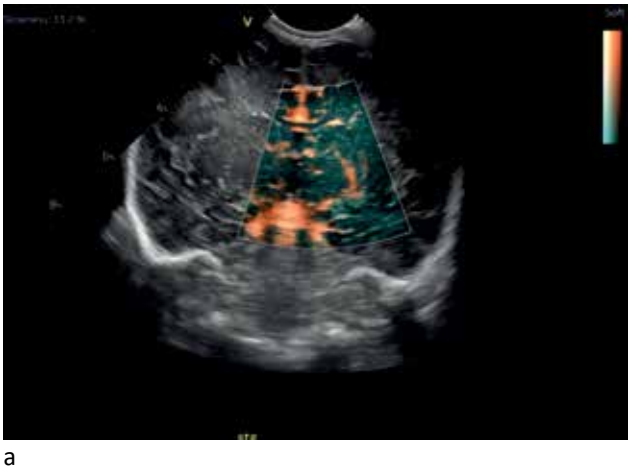
Another physiologic variant is represented by the course of the artery being divided into 3 types: type I which presents a superior course, type II an anterior course and type 3 a posterior course. Usually, LSA is distributed to the posterior components of the basal ganglia while the RAH is responsible for the medial and anterior extremities but due to the existence of physiologic variants diversity, the blood supply can be done differently [5,8,13].

In some cases, RAH might represent the unique blood supplier for the nucleus accumbens [5-7,14]. LSA are seen as end arteries (“perforating arteries”), hence being prone to hypoxia [5,15,16].

EMBRYOLOGY

During gestation, in days 28 to 30 of intrauterine life the primitive olfactory artery appears from the internal carotid artery and will further grow towards the olfactory bulb branching into what will be known as the RAH and after branching it will continue with the anterior cerebral artery. Over time, the anterior side of the circle of Willis will be formed by the anterior communicating artery which originates from the distal anterior cerebral artery.

Around days 34-36 of intrauterine life, the middle cerebral artery appears from the internal carotid artery and in its evolution, it will give birth to the cortical branches as temporal and frontal lobes are forming and the lateral fissure appears [5,17-19].



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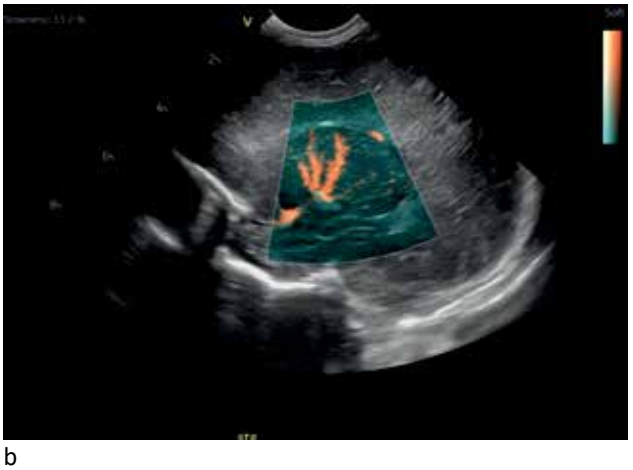

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FIGURE 1. Lenticulostriate vessels – Ultrasound Power Doppler Images – Observe origin from the middle cerebral artery

PATHOPHYSIOLOGY

The etiology and pathophysiology regarding the apparition of LSV are still under debate due to the multitude of risk/predisposing factors either of infectious or non-infectious origin. Moreover, LSV might represent just a transient episode in the population of the disease-free preterm population [16,20-22].

It has been suggested that late-onset LSV (>7 days of life) and early-onset LSV (<7 days of life) were attributed to perinatal injury in the case of the former or an in-utero injury for the latter [21]. Due to their caliber, smaller deep penetrating arteries are more prone to injury caused by hypoxic-ischemic events and infection, implying the fact that the inflammation pathway might lead to the appearance and progression of the vasculitis and the appearance of (subendothelial) basophilic deposits with or without iron ("mineralization") or diffuse microcalcifications. However, this might not be the rule and further research is still needed [5,20,21,23].

LENTICULOSTRIATE VASCULOPATHY AND CONGENITAL INFECTIONS

Congenital infections caused by T. Gondii, Rubella, CMV, HIV, or Treponema Pallidum most often have no signs after birth. Clinical evidence of intrauterine infections caused by tissue damage or physiologic changes may manifest after birth or after an amount of time (months years), the main predictive factor of severity being gestational age [24].

From the first description of the disease to the present, the perspective on this vascular pathology has undergone changes. In the last three decades, the focus on the etiology of LSV has been divided in two directions: congenital infectious causes (CMV, Toxoplasma Gondii, Rubella, HIV, Varicella, Treponema Pallidum, Meningitis) and non-infectious causes (Hypoxic ischemic conditions, Chromosomal abnormalities, fetal alcohol exposure, maternal drug abuse, maternal diabetes, twin-to-twin transfusion syndrome) [16].

1. CMV and lenticulostriate vasculopathy

Human Cytomegalovirus constitutes a group of agents in the herpesviruses family, with characteristic cytopathology of greatly enlarged (cytomegalic) cells containing intranuclear and cytoplasmic inclusions [24].

Although congenital cytomegalovirus (cCMV) is the leading cause of congenital infection, affecting about 1% of all live births worldwide [25], the prevalence of ultrasonographic findings in infants with cCMV, and its prognostic significance, has not yet been determined.

Lenticulostriate vasculopathy was initially described as an abnormally increased periventricular echogenicity in a case report of an infant with congenital CMV infection [26]. A few years later, Teele et al, described for the first time the relationship between LSV and vascular pathology, referring to this condition as "mineralizing vasculopathy" while analyzing a series of 12 neonates, 8 of them with positive congenital infections as: CMV, rubella and syphilis [27]. Congenital infections were considered to be the cause of echogenic stripes in the basal ganglia at the location of lenticulostriate arteries by Ben-Ami et al., suggesting that in all cases of neonates with suspected or proven intrauterine infections, especially with CMV and Rubella, routine head sonography should be performed, regardless of the symptoms [28].

In CMV infection symptoms can be detected at birth in 10–15% of the congenitally infected of which 50–90% will develop sequelae, the most frequent being sensorineural hearing loss [25]. LSV can be considered a common finding in infants with symptomatic congenital CMV infection and a sign of central nervous system involvement. LSV - as a solitary finding or in addition to other ultrasonographic findings is a possible marker of high risk for sensorineural hearing loss in infants with congenital CMV infection [29,30]. Antiviral treatment with valganciclovir (or ganciclovir if oral therapy is not possible) has been shown to preserve hearing in infants with symptomatic cCMV disease and central nervous system involvement, infants with isolated LSV and cCMV being also candidates for antiviral treatment according to many experts [16].

2. Toxoplasma Gondii and lenticulostriate vasculopathy

Toxoplasma Gondii is a protozoal parasite, ubiquitous in nature, causing a variety of illnesses that can be devastating for the fetus and newborn [24]. The etiologic significance of congenital infectious with T. Gondii in the possible development of, at that time, HTBG- Hyperechogenicity of basal ganglia, was first described by Cabanas F et al. [31].

T gondii infection causes vascular changes, especially in small arterioles, venules and capillaries, inducing congestion of the vessels and infiltration of large amounts of lymphocytes, plasma cells, macrophages, and eosinophils [24]. The result of the vascular anomalies and microbial proliferation have a radiologic correspondence consisting of abnormal parenchymal echogenicity, ventriculomegaly, calcifications, multicystic encephalomalacia, subependymal cysts, and the "candlestick" sign. The "candlestick-like" strips are an echo density of the lenticulostriate branches of the middle cerebral artery located in the region of the thalamus and the basal ganglia [29]. In congenital toxoplasmosis, the "candlestick" sign was firstly described by Volka et al. with echographic diagnosis in 3 cases (n=1 confirmed, n=2 possible) [32].

3. Other infectious causes

Most patients with congenital rubella syndrome (CRS) have central nervous system alterations, Rorke et al. reported that all infants with CRS had vasculopathy, with the destruction of the vessel walls by deposits of amorphous material, located mostly in the basal ganglia [33,34]. Although non-specific for CRS, linear hyperechogenic basal ganglia lesions were a common finding in a 5 cases report conducted by Ying-Chao Chang et al. [35].

Other infectious circumstances in LSV's etiology have included sporadic cases of syphilis [27,28,36], varicella [36,37], meningitis [37], and HIV [38].

HYPOXIC–ISCHEMIC CONDITIONS

Although congenital infections were initially considered the primary cause of LSV, it is now clear that many other conditions are associated with LSV [37].

Initially, LSV was considered as associated with Cytomegalovirus; however, this association was extended to include other congenital infections, and then further include non-infectious etiologies [39]. These etiologies comprise asphyxia, hypoxic-ischemic conditions [23,36,37] ischemic brain infarct [40], chromosomal anomalies [23,27,36,37,41,42], fetal alcohol exposure [37], maternal drug abuse [23,31,36,37], congenital anomalies [43], neonatal lupus erythematosus [44,45], maternal diabetes [46], congenital heart disease [23], twin–to-twin transfusion syndrome [47], and congenital hypothyroidism [48].

The immature brain demonstrates areas of selective vulnerability to various insults, including hypoxia-ischemia [49]. The basal ganglia and thalamus are highly vulnerable to hypoxic-ischemic injury, and it 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 [50]. In the absence of a rich capillary network, this pronounced autoregulatory 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 the basal ganglia and thalamus [51,52]. Repeated episodes of hypoxia–asphyxia induced by intermittent cord occlusion disproportionately injure the striatal GABAergic neurons that are plentiful in the basal ganglia of the fetal sheep brain [53]. 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 [49] described a phenomenon referred to as "ferrugination" or "fossilization" of neurons in areas of ischemic injury.

Severe diffuse hypoxic–ischaemic encephalopathy in neonates initially results in a central pattern of damage, involving deep grey matter (basal ganglia and thalami), but with prolonged ischemia, the cortex can also become involved. Ultrasound could appear normal in the beginning or could reveal a mild global increase in echogenicity of the brain with or without diffuse edema obliterating the cerebrospinal fluid spaces. Increased echogenicity of the thalami suggests more severe injury and is associated with a poorer outcome [51]. Doppler examination of the anterior and middle cerebral arteries has been employed in the setting of suspected hypoxic-ischemic encephalopathy, with a resistive index of less than 0.6 associated with poor outcomes, even if other sonographic signs are absent [50].

A retrospective study published in 2000 examined sixty-three cases of lenticulostriate vasculopathy in which thirty-three patients had hypoxic-ischemic conditions considered to be the principal contributory factor in the development of LSV. This includes perinatal asphyxia events, pulmonary disease and cyanotic heart disease - five patients had a perinatal asphyxia event and a prolonged course due to pulmonary disease, five patients with perinatal asphyxia that has no significant underlying lung disease with the exception of one patient who had mild respiratory distress syndrome and developed E.coli pneumonia. Ventilatory support in this group was required for a mean of 5,8+/-3,8 days [23].

CURRENT DIAGNOSTIC METHODS

The cUs are the best method for detecting neonatal lenticulostriate vasculopathy.

LSV was first described 30 years ago, on a cUS obtained on a second-born twin (BW=1240g) with CMV infection [26].

The bright, hyperechogenic lines, represented by lenticulostriate branches of middle cerebral arteries, located in the region of the thalamus and basal ganglia, are different from echogenicities associated with calcifications [27]. However, some hyperechogenic lines can be represented by reflections of normal lenticulostriate arteries, so overinterpretation of echogenic linear lenticulostriate vessels as LSV may be possible [20,46].

LSV can be either unilateral or bilateral, with the presence of linear or branching hyperechogenic le-

sions in both coronal and parasagittal views [31,54]. Vessel patency can be confirmed by color Doppler US examination [28,31,42].

Several cranial ultrasound classification systems were proposed. Shin H et al. proposed the existence of low-grade and high-grade LSV, notions which were defined by the number of affected striations. A number of <3 branches were considered low grade whereas a number of ≥3 branches was considered high grade [55].

In the case of patients with CMV, Hong SY et al. split the LSV cases into mild or severe taking into consideration the number of affected vessels and the diameter of the vessels. A severe LSV is represented by at least one line ≥ 2.5 mm, whereas the mild form was represented by lines < 2.5 mm in diameter [39].

In a longitudinal cohort study done on the very low-birthweight preterm population, Hung YL et al. suggested the terms "punctate type", "branching type" and "linear type" to describe the hyperechoic images seen on ultrasound [56].

Sisman et al. proposed a new classification based on the hyperechoic image generated by cranial ultrasound in parasagittal view. The hyperechoic image of the Sylvian fissure was taken as a standard for measurements. As a result, 4 stages were identified: stage 0 – no visible vessel (figure 2); stage 1 – a single lenticulostriate artery with soft linear echogenicity (figure 3); stage 2 – the vessels are more hyperechoic (figure 4); stage 3 – vessels are of the same echogenicity with the standard (figure 5) [16].

There are a few studies that have focused on the MRI as a diagnostic method for LSV [57]. Fabre et al. used cerebral MRI data in terms of perinatal factors and neurodevelopmental follow-up. The white matter (WM) and basal ganglia (BG) apparent diffusion coefficients (ADC) have been measured. The results showed a higher ADC score in the high-grade LSV versus the low-grade LSV, explained by the decreasing ADC in the BG at the same time as maturation, so a delay in maturation encountered in the pathogenesis of LSV may be an argument for that [58,59]. As a result, not all newborns with low-grade LSV gain an

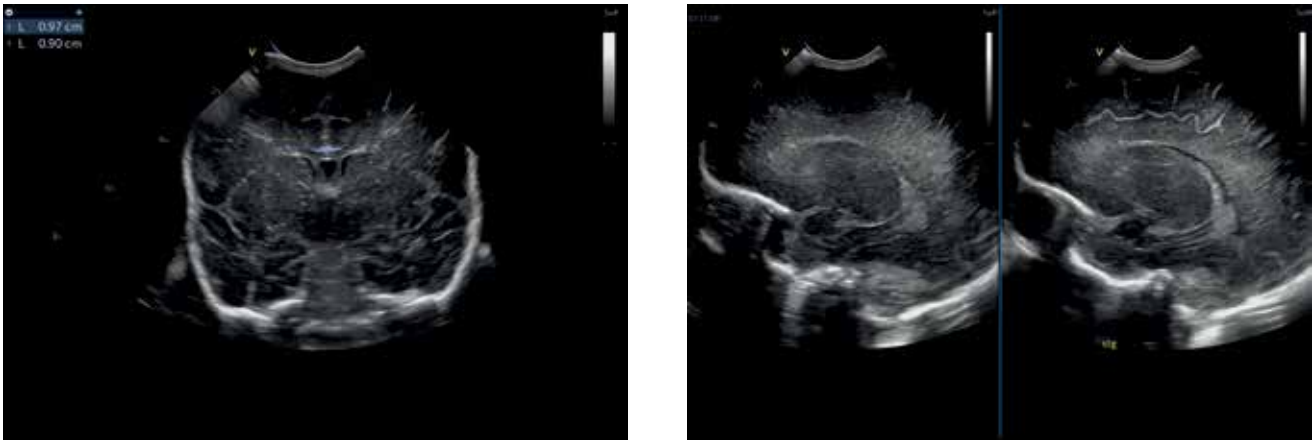

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FIGURE 2. Structures of normal ultrasound appearance, without signs of lenticulostriate vasculopathy (stage 0)

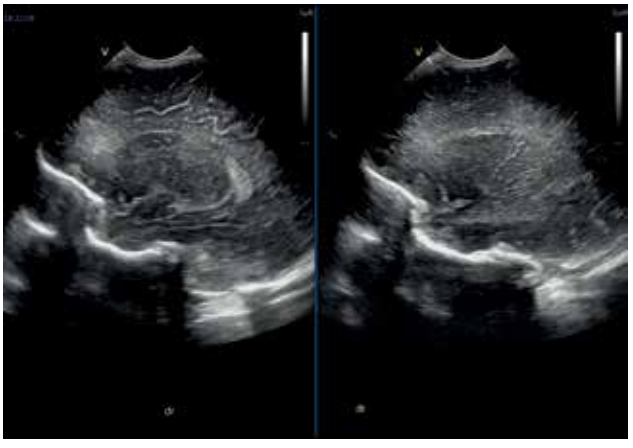


FIGURE 3. Lenticulostriate vasculopathy – stage 1. Single vessel on the right. Asymptomatic neonate.

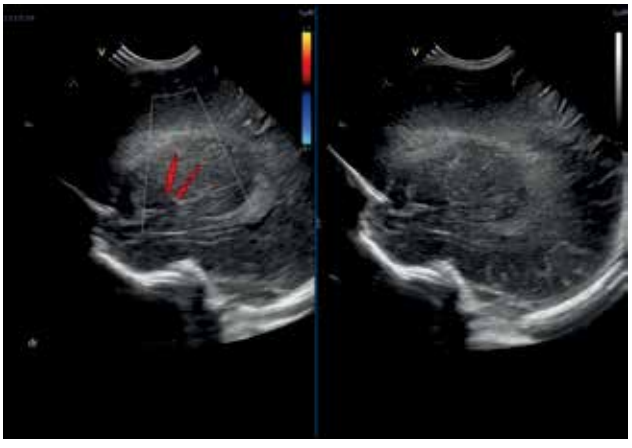
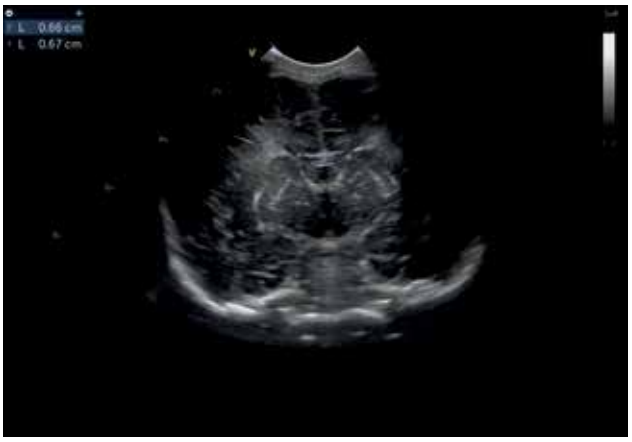


FIGURE 4. Stage 2 lenticulostriate vasculopathy Neonate with CMV seroconversion during pregnancy. No CMV was isolated from the neonate(blood and urine samples). Small linear images corresponding to vessels – Color Doppler image on the left; B mode image on the right



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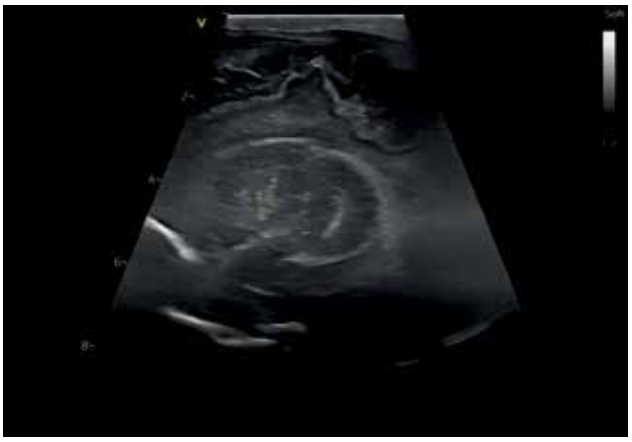

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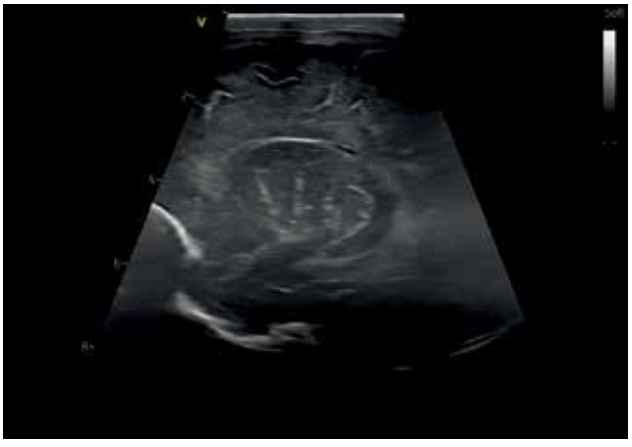

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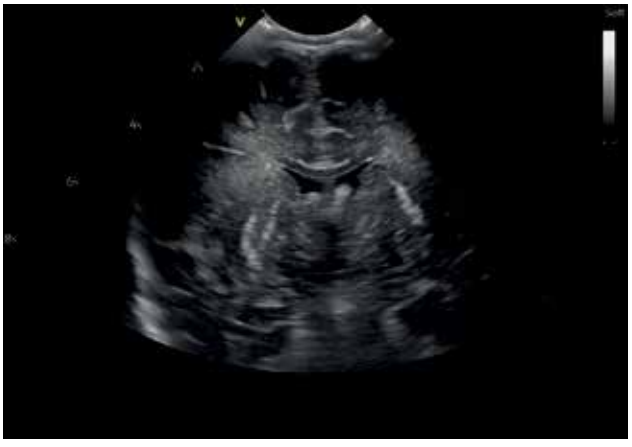

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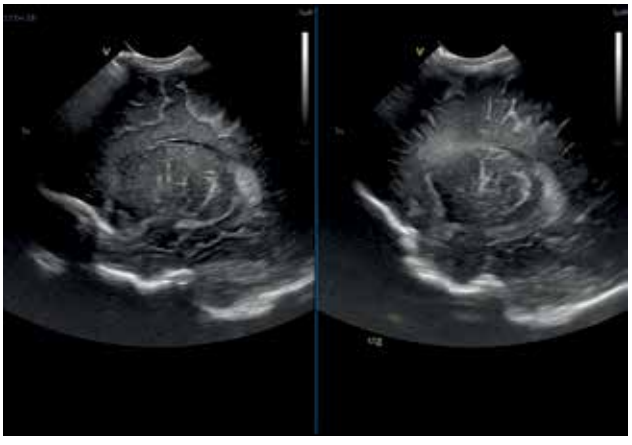

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FIGURE 5. Stage 3 Lenticulostriate vasculopathy – gross linear hyperechogenicity. Premature infant 35 weeks with respiratory distress a. Coronal image – observe bilateral linear opacities; 5b, 5c. Parasagittal images – linear probe – linear opacities bilateral; 5d. Same patient at 3 months – coronal section; 5e Same patient at 3 months – parasagittal section

advantage from having a cerebral MRI at a later date, but the ones with high-grade LSV require an MRI. Added to that, those with increased ADC on the MRI need a close neurological follow-up [58].

CONCLUSIONS

Lenticulostriate vasculopathy represents a pathology known for a long time and frequently overlooked. While in the past it was considered mainly associated with chronic intrauterine infections, at present, it is more and more seen as a consequence of perinatal hypoxic events, especially in premature neonates. Further large follow-up studies are needed in order to better characterize the etiology and prognosis of this pathologic condition.

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