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The Mammillary Bodies: A Review of Causes of Injury in Infants and Children

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ABSTRACT

SUMMARY: Despite their small size, the mammillary bodies play an important role in supporting recollective memory. However, they have typically been overlooked when assessing neurologic conditions that present with memory impairment. While there is increasing evidence of mammillary body involvement in a wide range of neurologic disorders in adults, very little attention has been given to infants and children. Literature searches of PubMed and EMBASE were performed to identify articles that describe mammillary body pathology on brain MR imaging in children. Mammillary body pathology is present in the pediatric population in several conditions, indicated by signal change and/or atrophy on MR imaging. The main causes of mammillary body pathology are thiamine deficiency, hypoxia-ischemia, direct damage due to masses or hydrocephalus, or deafferentation resulting from pathology within the wider Papez circuit. Optimizing scanning protocols and assessing mammillary body status as a standard procedure are critical, given their role in memory processes.

ABBREVIATIONS: CCHS = congenital central hypoventilation syndrome; HIE = hypoxic-ischemic encephalopathy; LiTT = laser interstitial thermal therapy; MB = mammillary body; MTS = mesial temporal sclerosis; SVHD = single ventricular heart disease

The mammillary bodies (MBs) were arguably the first brain region to be implicated in memory, on the basis of the pathology observed in Korsakoff syndrome around the end of the 19th century. However, since then, they have been consistently overlooked during neuropathologic assessments, with memory impairment often being attributed to hippocampal involvement. More recent studies have re-confirmed the importance of the MBs for memory in adults. Furthermore, it has been demonstrated that MB pathology is by no means restricted to Korsakoff syndrome/thiamine deficiency but can occur in numerous neurologic conditions, including strokes, craniopharyngiomas, colloid cysts, schizophrenia, Alzheimer disease, multiple sclerosis, and following acute or repetitive/prolonged hypoxia.

Despite this wide-ranging involvement of the MBs in neurologic disorders in adults, far less attention has been given to the MBs in infants and children. However, several recent studies have underlined the importance of assessing the MBs in younger patients. For example, the MBs appear particularly sensitive to neonatal hypoxia-ischemia. Volume loss in the MBs, the hippocampus, and fornices, is also associated with cognitive impairment, including episodic memory deficit in school-age children with a history of neonatal hypoxic-ischemic encephalopathy. MB atrophy has also been reported following the Fontan procedure, with MB volume related to the degree of memory impairment.

These recent studies have identified the importance of assessing the status of the MBs in infants and children, and as with adult cases of MB pathology, there is likely a wide range of conditions that can impact the MBs in younger patients. This review will identify those conditions in which MB pathology has been observed in infants and children. The focus is on human literature and includes studies that reported MB pathology on brain MR imaging in children (see the Online Supplemental Data for an overview of search terms and inclusion criteria and the list of articles identified). The conditions associated with MB pathology will be summarized below as well as implications for radiologic assessment.

Mammillary Body Embryology, Anatomy, and Function

The MBs are a paired round structure located at the undersurface of the diencephalon. They are separated along the midline by the

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intermammillary sulcus. The MBs contain 2 gray matter structures, the medial and lateral nuclei; these are encapsulated by white matter and form the mammillothalamic and mammillotegmental tracts.

In humans, both the lateral and medial mammillary bodies are present at 10 weeks’ gestation, though at this stage, the cells are undifferentiated. By 11–14 weeks, the MBs comprise a group of homogeneous neurons; by 16 weeks’ gestation, they are clearly differentiated. By 24–33 weeks, the MBs take on an appearance similar to that in adult MBs, ie, they are well-developed at the time of full-term birth.

There is some natural variation in the anatomy of the MBs in the general population. In the axial plane, they can appear more circular or elliptic, and there is also variation in the depth of the intermammillary sulcus. The MBs can also appear asymmetric without an underlying pathologic cause; for example, Tagliamonte et al reported MB asymmetry in 13.9% of their young, healthy cohort. In most cases, this asymmetry arose from the abnormal course of the posterior cerebral artery, which resulted in dorsal displacement of the MBs. In 4 of the 78 participants, the asymmetry appeared to reflect a loss of volume of one of the MBs.

In addition to primary damage, the MBs can be affected by damage to their principal input and output (Fig 1). For example, anterograde degeneration can occur following injury to the hippocampus or fornix, though the resultant MB atrophy is thought to reflect a loss of white matter rather than neuronal loss. In contrast, neuronal loss in the MBs can occur as a result of retrograde degeneration following damage to the mammillothalamic tract.

Consistent with the anatomic connectivity of the MBs with the hippocampus, fornix, and mammillothalamic tract, the MBs also form a functional network with these structures, ie, the Papez circuit (Fig 1). The MBs have an important role in integrating input from the hippocampus and the Gudden tegmental nuclei and for coordinating oscillatory activity in the hippocampus and cortex. The MBs appear to be particularly important for episodic (ie, event) memory, including temporal and contextual memory.

**MB Pathology**

**Thiamine Deficiency.** Korsakoff syndrome, arising from thiamine (vitamin B1) deficiency, is the most common condition associated with MB pathology. Indeed, almost half of the articles identified in this literature search referred to MB abnormalities in children with thiamine deficiency. Although Korsakoff syndrome is typically associated with alcoholism in adults, many other conditions have been identified that can result in similar thiamine deficiency and resultant neuropathology in children.

Thiamine deficiency may present as infantile encephalopathic beriberi (dry beriberi) or as Wernicke encephalopathy. Wernicke encephalopathy is difficult to diagnose and often goes untreated in clinical practice. This lack of detection and treatment is evidenced by the finding that Wernicke encephalopathy is first diagnosed postmortem in >80% of cases in adults and >40% in children. Because patients usually respond well to acute thiamine replacement therapy, it highlights the importance of making an early diagnosis.

Wernicke encephalopathy in children typically arises from nutritional deficiency, which can occur due to vomiting (eg, due to anorexia nervosa, hyperemesis, gastrointestinal obstruction), chronic gastrointestinal disease, and following bariatric surgery. Wernicke encephalopathy has also been reported following acute liver failure and pancreatitis. The MR imaging characteristics of thiamine deficiency include symmetric T2 hyperintensities in the dorsal medial thalamus, MBs, periaqueductal gray matter, and tectal plate, with the MBs being involved in 17%–58% of cases. High-signal-intensity changes on T2-weighted images are the most frequent pathologic findings seen on MR imaging compared with low-signal-intensity changes on T1-weighted images.

Contrast enhancement of the MBs, which is characteristic in alcohol-related Wernicke encephalopathy, occurs less frequently in
Wernicke encephalopathy in nonalcoholic populations.\textsuperscript{39,40} However, contrast enhancement has also been reported in children with Wernicke encephalopathy, resulting from malnutrition, for example.\textsuperscript{31,33} In addition to signal changes, MB volume loss has also been reported in patients with anorexia nervosa as well as recovery of MB volume in individuals who regained weight.\textsuperscript{30} Recovery of MB volume has also been reported in patients with acute liver failure following treatment with thiamine.\textsuperscript{35} Furthermore, MB volume was found to correlate with blood thiamine levels.\textsuperscript{32} Consistent with this observed recovery of MB volume after thiamine treatment, signal changes in Wernicke encephalopathy have also been shown to improve\textsuperscript{41} or even resolve after treatment.\textsuperscript{26,38} This finding suggests that the signal changes may reflect reversible vasogenic edema as opposed to acute ischemia.\textsuperscript{32}

MB Pathology in Infants with Perinatal Asphyxia. Severe perinatal asphyxia can result in hypoxic-ischemic encephalopathy (HIE). The prevalence of HIE is approximately 1.5 per 1000 live-birth-term neonates.\textsuperscript{42} The brain areas that are typically involved in HIE include the deep gray nuclei or white matter and cortex, depending on the severity and duration of the insult. Two main patterns of injury have been distinguished on MR imaging.\textsuperscript{43} The first is the basal ganglia–thalamus pattern, which is mainly associated with acute, severe perinatal asphyxia such as uterine rupture; the second is the watershed-predominant pattern of injury, which is more common after prolonged partial asphyxia. This second pattern involves the vascular watershed zones of the anterior MCA and posterior MCA. In the most severe cases, both patterns are visible—this is called a "near total" pattern of injury because on diffusion-weighted MR imaging, the cerebellum is mostly spared.

The limbic system can also be affected following HIE, with MRIs showing diffusion restriction on DWI in the hippocampal region.\textsuperscript{44,45} Recent studies have also shown signal change in the MBs after perinatal asphyxia (Fig 2).\textsuperscript{12,13} Molavi et al.\textsuperscript{12} reported a hyperintense signal change in the MBs on the T2-weighted sequences in 13.2% of neonates with HIE. In those cases with abnormal MB signal, the most common MR imaging pattern (in 41.9% of cases) was found to be abnormal signal on either T2-weighted imaging or DWI restricted to the MBs, with no other abnormalities observed. Lequin et al.\textsuperscript{13} performed a multicenter study looking into signal changes on both T1- and T2-weighted images as well as restricted diffusion on DWI in the MBs after HIE and therapeutic hypothermia. They observed abnormal MB signal in approximately 40% of the cooled neonates. Involvement

\textbf{FIG 2.} Images from a term neonate initially scanned at 6 days of age. A, A T2-weighted image with a hyperintense aspect of the MBs. B, A \(b=1000\) image shows a hyperintense aspect on the ADC map (not shown), consistent with ischemia. C, Ischemia is also seen symmetrically in the thalami and basal ganglia. Follow-up at 3 months shows atrophy of the MBs (D) with flattening on the sagittal view (E). Tissue loss and gliosis in the lentiform nucleus can also be seen (F).
of the MBs was not related to the severity of encephalopathy or the severity of hypoxic-ischemic brain injury, and there was no pattern to the relation of brain injury. In both studies, the MB abnormalities were only identified retrospectively, when the MBs were specifically assessed. Thus, it is likely that many infants with MB abnormalities are currently being overlooked, with their MRI findings reported as looking normal. These results emphasize the need for optimized protocols with sufficiently thin section series (<2 mm) and for the MBs to be routinely assessed.

Annink et al\(^\text{14}\) performed a retrospective observational study of neonates with HIE with follow-up at 10 years of age. Of the infants with abnormal neonatal MBs, 76% had MB atrophy at 10 years of age. MB atrophy was seen in 38% of all 10-year-old patients (50% of those who had undergone therapeutic hypothermia and 17% of those who not had hypothermia treatment). The study also showed that children with a history of HIE have long-term neurodevelopmental problems despite therapeutic hypothermia. Hippocampal volume and MB atrophy were strongly associated with neurocognitive outcome and episodic memory at 10 years of age. These findings suggest that abnormal T2 signal of the MBs in the acute phase is associated with cognitive and memory deficits later in life.

Dzieciol et al\(^\text{46}\) assessed children and adolescents with developmental amnesia, which is marked by extensive bilateral damage to the hippocampus as a result of early life exposure to hypoxic-ischemic events. Developmental amnesia is characterized by impaired episodic memory with relative sparing of semantic memory.\(^\text{57}\) Dzieciol et al found the MBs absent in 12 of the 18 patients with developmental amnesia. The remaining 6 patients had visible MBs, but as a group, they were significantly smaller than those in controls. Of note, all 12 patients in whom the MBs were absent experienced a hypoxic-ischemic event perinatally, whereas for the 3 patients who experienced the hypoxic-ischemic event later in life (4–15 years of age), the MBs were visible. Geva et al\(^\text{46}\) also noted that the MBs were small in 10 of their 20 patients with hippocampal atrophy resulting from perinatal hypoxia-ischemia.

**Congenital Central Hypoventilation Syndrome.** Congenital central hypoventilation syndrome (CCHS) is defined as the failure of automatic control of breathing, with ventilation most severely affected during quiet sleep, when automatic neural control is predominant.\(^\text{49}\) CCHS can disrupt blood pressure, glucose and temperature control, reduce the sensitivity to carbon dioxide and oxygen, as well affect intestinal motility causing malabsorption.\(^\text{50}\) Patients with CCHS often show multiple cognitive impairments including learning and memory problems.\(^\text{51,52}\) Initial studies on this patient group reported structural and functional changes in the hippocampus and anterior thalamus.\(^\text{53–55}\) In a subsequent study, Kumar et al\(^\text{56}\) found the MBs and fornix volume to be significantly reduced in patients with CCHS, suggesting that pathology within the Papez circuit, including the MBs, contributes to the memory impairment observed in this patient group.

Although only 1 study has examined the MBs in patients with CCHS, the pathology appears similar to that of other sleep-disordered breathing conditions such as obstructive sleep apnea as well as heart failure and beriberi. In addition to the chronic hypoxia/hypoxemia present in these conditions, patients can also present with intestinal absorption abnormalities as well as low levels of thiamine and magnesium,\(^\text{57,58}\) which are likely to contribute to the pathology in these patient groups.

**Congenital Heart Disease.** Single ventricular heart disease (SVHD) is considered one of the most challenging types of congenital heart disease, with an incidence of approximately 1 per 2000 live births.\(^\text{59}\) Patients typically require at least 3 staged palliative operations; the Fontan procedure has the greatest impact on life expectancy. Patients with SVHD are at greater risk of brain injury and neurocognitive deficits as a direct result of the condition and comorbidities\(^\text{60}\) as well as from the multiple surgical procedures.\(^\text{61}\) Adolescents with SVHD exhibit brain lesions on MR imaging in approximately 60% of cases.\(^\text{62}\) This finding could be due to the delayed brain maturation observed in complex heart disease, which can make the brain more vulnerable to injury.\(^\text{63}\)

Cabrera-Mino et al\(^\text{15}\) found reduced MB volumes in adolescents with SVHD compared with controls. Cognitive test scores were also significantly lower in the SVHD group, and performance on verbal and delayed recall memory tests correlated with MB volume, ie, poorer memory with smaller MBs. In a related study, Singh et al\(^\text{64}\) investigated DTI-based diffusivity measures. Multiple brain regions including the limbic system and MBs showed changes consistent with chronic tissue injury. Given that the MRIs in this study were acquired more than a decade after the patient’s last surgical procedure, the assumption was that the pathology reflected chronic changes associated with this condition, predominantly to myelin.

**Metabolic Disease.** MB abnormalities have only been reported in a few metabolic diseases. One case showed diffusion restriction in the MBs in a patient with Leigh disease arising from a mutation in the sulfide:quinone oxidoreductase enzyme.\(^\text{65}\) A further case showed enhancement in the MBs in a patient with Alexander disease,\(^\text{66}\) while Inui et al\(^\text{67}\) found high signal intensities on T2-weighted images in the MBs of a young patient with a case of chronic infantile fucosidosis. Finally, 2 patients with bitiondase deficiency were reported showing bilateral abnormal signal intensity in the MBs and area postrema of the dorsal medulla as well as bilateral symmetric optic neuritis.\(^\text{68}\)

**Epilepsy.** There is a well-documented relationship between MB abnormalities and epilepsy in adults. As will be discussed in the next section, patients with refractory mesial temporal lobe epilepsy often undergo temporal lobe surgery or laser interstitial thermal therapy (LiTT) as part of their treatment. The resultant hippocampal loss can cause anterograde degeneration in the MBs. There is some evidence that the MBs may also be implicated in epilepsy before treatment, possibly due to anterograde degeneration from the pre-existing hippocampal pathology or as a more direct effect of the epilepsy.\(^\text{69}\) Indeed, a case from our own hospital demonstrates this finding of compromised MBs in a patient with epilepsy who had not undergone temporal lobe surgery or LiTT (Fig 3).

**Mesial Temporal Sclerosis.** Mesial temporal sclerosis (MTS) involves neuronal loss and gliosis of the hippocampus and is the
most common disease associated with mesial temporal lobe epilepsy. MB and fornix asymmetry have been repeatedly reported in MTS. Ozturk et al found asymmetry of the MBs (37.1% of cases) and fornix (34.3% of cases) when examining patients with MTS presurgery. This reported asymmetry was significantly higher than that found in a control group (6.5% for MBs and 7.9% for fornix). Kim et al performed a similar study but observed asymmetric MBs in only 3% of patients with MTS presurgery. This discrepancy may be due to Ozturk et al using 1.5-mm slices to evaluate the MB asymmetry compared with 3-mm slices in the Kim et al study, increasing the likelihood of detecting asymmetries.

Refractory mesial temporal lobe epilepsy is the most common form of surgically treated epilepsy and is caused by MTS in ~65% of the patients undergoing surgery. In a blinded retrospective analysis of 20 patients who underwent amygdalohippocampal LiTT, the seizure-free group showed an average 35% reduction in ipsilateral MB volume compared with 8% reduction in patients with continued seizures. This finding suggests that MB volume change could be a marker for successful ablation surgery. In contrast, Urbach et al did not find MB volume after amygdalo-hippocampectomy predictive of postsurgical seizure outcome in patients with unilateral MTS. Because the latter study involved twice the number of patients, there might be a selection bias in the former study; alternatively, the discrepancy could reflect differences between LiTT and amygdalo-hippocampectomy.

Epilepsy Related to MB Pathology. Mamourian and Brown reported a case study of a 4.5-year-old boy who presented with staring spells and abnormal electrocardiogram activity in the right parietal region. MR imaging showed a total absence of the right MB, while the temporal lobes appeared normal. The authors raised the possibility that the seizure activity was related to the shrunken right MB. There have been other studies that have directly linked the MBs to epileptic activity rather than being indirectly affected via the hippocampus. For example, epileptiform discharges have been recorded directly from the MBs, and a fluorodeoxyglucose PET/CT study of a 50-year-old woman found the MBs to be the focus of epileptic activity.

Further associations between the MBs and seizures come from an adolescent with a 2-year history of complex partial seizures whose MR imaging showed encephalomalacia in the right anteromedial thalamus, glosis of the mammillothalamic tract, and a rightsided atrophic MB. The mammillothalamic tract and MB pathology were thought to be the result of retrograde degeneration following a thalamic infarct. Because there was no evidence of hippocampal involvement, the partial seizures were assumed to be due to the mammillothalamic pathology.

Hypothalamic hamartomas can also be associated with epilepsy; Freeman et al found that the common factor in a large group of patients who presented with hypothalamic hamartoma and epilepsy was involvement of the MBs, suggesting that they may be the focus of the epileptic activity. Linear defects in the anterior thalamus and associated MB and fornix atrophy have also been identified in patients with chronic seizures.

One further study reported congenital aplasia of the MBs in a young child with early infantile epileptic encephalopathy (Ohtahara syndrome), who also presented with dentato-olivary dysplasia. The absence of the MBs, both macroscopically and microscopically, was noted at postmortem examination, leading the authors to recommend high-resolution MR imaging and detailed postmortem assessment in this patient group.

Masses Involving the Hypothalamic Region, Postoperative MB Abnormalities, and Other Iatrogenic Causes of MB Pathology. The MBs can be displaced and/or compressed in numerous conditions that result in masses forming in adjacent structures, for example, hypothalamic hamartomas and suprasellar arachnoid cysts. The MBs are an important landmark for neurosurgeons when operating on these suprasellar masses. Although compression occurs, the structure of the MBs can remain intact and after decompression, the MBs can appear normal.

Craniopharyngiomas are rare embryogenic malformations of the sellar/parasellar area with low-grade histologic malignancy. Despite high survival rates, the quality of life can be affected by optic chiasm and hypothalamic pathology, resulting in visual impairment and hypothalamic obesity, respectively. In a mixed population of pediatric and adult patients with craniopharyngiomas, the authors classified the MBs as “dislocated” in 34% of cases and “unrecognizable” in 19% of cases. Involvement of the MBs was one of the main factors associated with postoperative obesity. This was in accordance with Müller et al, who found that the extent of hypothalamic damage increased the risk of postsurgical obesity in a group of 120 children. In addition to the development of hypothalamic obesity, children with high-grade hypothalamic involvement also showed poorer performance on tests of executive function and reduced functional capabilities for daily life actions, and these cognitive impairments appear to be associated with MB involvement.

The MBs can be directly affected by not only these masses but also the treatment protocols, including radiation therapy and chemotherapy, likely causing additional MB damage. For example, intrathecal chemotherapy for childhood acute lymphoblastic

FIG 3. Ti-weighted images show generalized atrophy of the brain with atrophy of the MBs, which are completely flattened (A and B), and ex-vacuo dilation of the ventricles (C) in a 2.5-year-old patient with severe epilepsy.
leukemia has been shown to affect the MBs. Ciesielski et al found the MBs and prefrontal cortex significantly reduced in volume in the patient group with acute lymphoblastic leukemia compared with matched controls. The patient group also performed significantly worse on both visual and verbal memory tasks.

Personal Experience
In our institution (Wilhelmina Children’s Hospital), as a standard practice, we use imaging protocols that enable us to visualize the MBs in detail. Furthermore, the MBs are routinely assessed in all pediatric MRIs of the brain. This practice has resulted in MB pathology being observed in conditions that have not previously been reported in the literature. For example, when assessing the scans of neonates with an MCA infarct, we have identified several cases with damage to the MBs. One example involved a girl with hereditary spherocytosis who was severely anemic at 6 weeks and presented with right-sided hemiparesis at 2 months of age. A scan at 1 year of age showed sequelae of a large left-sided MCA infarct with little remaining basal ganglia and left-sided atrophy of the body of corpus callosum, thalamus, hippocampus, and MB (Fig 4).

Chronic bilirubin encephalopathy (kernicterus) can also cause bilateral MB abnormalities. A term neonate with an uneventful pregnancy and an uncomplicated delivery was admitted for an exchange transfusion for severe hyperbilirubinemia. The patient showed opisthotonus and convulsions/seizures. A brain MR imaging at 8 days of age showed a bilateral hypointense aspect of the MBs on T1-weighted imaging and a hyperintense T2 aspect in addition to a T1 hyperintense aspect of the globus pallidus bilaterally, consistent with kernicterus (Fig 5). At a 7-month follow-up, the MBs appeared atrophic. To our knowledge, there are no other reports of MB involvement in kernicterus.

Hydrocephalus can often affect the MBs, causing compression and making them difficult to visualize. However, it is only possible to determine whether there is long-lasting structural damage to MBs after the onset of treatment and reduction of intracranial pressure. The MBs are at risk from direct pressure from hydrocephalus, which can reduce blood flow to the MBs and cause local ischemia, but also from the interventional treatment procedures. A 32-week preterm neonate was born with unilateral ventricular dilation at our institution. No MB abnormalities were observed on 2-day postnatal MR imaging. Because of the suspected obstruction at the foramen of Monro, a ventricular access device was inserted. MR imaging after 2.5 months showed atrophy with an abnormal signal intensity of the left MB (Fig 6).

We have also found the MBs to be affected by group B streptococcus, the leading cause of neonatal meningitis, and herpes simplex encephalitis. One such patient was scanned at 11 weeks after group B streptococcus sepsis and possible meningitis (Fig 7). On MR imaging, the basal ganglia appeared normal, but there was minor supratentorial generalized loss of white and gray matter with subtle dilation of the lateral ventricles, and both MBs were atrophic.
Finally, as previously described, metabolic disorders might also impact the MBs. From MR imaging studies, MB abnormalities have been described in Leigh disease, Alexander disease, and fucosidosis. A postmortem study, however, found necrosis and spongiosis of the MBs in a patient with methylmalonic acidemia.

Similarly, we had a patient with propionic acidemia who showed bilateral volume loss of the MBs on a 3-month follow-up scan. No MB abnormalities were seen on an initial scan at 2 weeks, but this may have been outside the window of the acute stage (Fig 8).

**DISCUSSION**

While the MBs have been implicated in a wide range of neurologic conditions in adults, their involvement in neurologic conditions in infants and children is less well-documented. Thus, we have performed a review of conditions in younger patients in whom MB pathology has been reported. Perhaps unsurprisingly, given that the MBs and their connections are well-developed at birth, many of the conditions that can cause MB pathology in adults also can affect the MBs in younger individuals.

While numerous diverse conditions have been associated with MB pathology across age groups, this pathology appears to typically arise from a limited number of factors: thiamine deficiency, hypoxia-ischemia direct damage due to masses or hydrocephalus, or deafferentation resulting from pathology within the wider Papez circuit.

MB pathology is most frequently associated with thiamine deficiency; indeed, MB pathology was first noted in Korsakoff syndrome at the end of the 19th century, and this provided the first link between the MBs and memory. However, the exact mechanism by which thiamine deficiency impacts the MBs remains uncertain. It is likely that the effects of thiamine deficiency are multifactorial, given that it can cause cell loss via various mechanisms, including mitochondrial dysfunction, glycolysis, acidosis, increased oxidative stress, excitotoxicity, and inflammation.

Suboptimal thiamine reserves or borderline thiamine deficiency can present in many conditions and can be exacerbated by glucose infusion, which is often given to children on hospitalization.

There is increasing evidence that the MBs are affected by hypoxia-ischemia, particularly in neonates. What is striking is that the MBs can often be the only structure to show abnormal signal, with the rest of the brain appearing normal, highlighting the sensitivity of the MBs.

Both thiamine deficiency and hypoxia can cause neural cell loss via the activation of several similar signaling pathways that result in necrosis and apoptosis. As with thiamine deficiency, hypoxia also increases mitochondrial dysfunction, excitotoxicity, oxidative stress, and acidosis.

Furthermore, both conditions disrupt the blood-brain barrier and alter levels of hypoxia-inducible factor 1α. Given the sensitivity of the MBs to thiamine deficiency and hypoxia, the most parsimonious conclusion is that the MBs are affected by similar underlying mechanisms in both conditions; however, as the cell loss likely occurs via multiple
complex mechanisms, there may be selective pathways that are preferentially involved in the different conditions and even across different patients with the same condition.

A further cause of MB pathology is via direct damage, eg, due to a mass, hydrocephalus, or radiation therapy, or indirectly via anterograde or retrograde degeneration. In adults, damage to the hippocampus or fornix typically results in a loss of white matter in the MBs, with a volume reduction of up to 50%.

However, it is possible that in neonates, the MBs are more sensitive to deafferentation, and greater atrophy might be observed following damage to the hippocampus or fornix. Direct damage to the MBs should be minimized when possible, for example, when targeting masses in the vicinity of the MBs. However, there are some inconsistencies as to whether compression of the MBs can cause long-term pathology once the pressure on the MBs is removed. Therefore, further work is needed to determine those situations in which the MBs are most vulnerable to both direct and indirect damage and the time windows during which long-term pathology can be avoided.

While damage to the MBs appears to arise from similar etiologies in adults, children, and infants, it is not yet clear whether age differentially affects the sensitivity of the MBs. There is some suggestion that neonatal brains are more resilient to some forms of damage, for example, those arising from hypoxia, because there are differing metabolic demands in cells and a different propensity to excitotoxicity. However, the blood-brain barrier is also immature during the neonatal period, which could exacerbate the impact of hypoxia and thiamine deficiency. Given the high rate of MB involvement in neonatal hypoxia-ischemia, it is possible that the MBs are more sensitive in this age group; however, it is difficult to directly compare with adults, given the difference in prevalence. Animal models may be required to determine whether MBs in neonates are more sensitive to hypoxia-ischemia as well as deafferentation.

The purpose of this review was to identify conditions in which MB pathology occurred rather than specifically address the functions of the MBs; indeed, most of the included studies described pathology but did not perform detailed cognitive tests. From the evidence that is available, however, it seems that little if any functional compensation occurs when MB pathology occurs earlier in life. In both children and adults, the profile of memory impairment seems remarkably similar, with episodic and recollective memory being particularly affected. However, there are very few cognitive assessments of individuals with early-acquired MB pathology in which the damage is selective. In most cases there is co-occurring pathology in the hippocampus, making it difficult to determine the specific contribution of the MBs. This issue highlights the need to assess the extent of memory impairment in cases in which pathology is restricted to the MBs.

A limitation of this review is that many of the studies comprise case reports. Furthermore, some of the studies included mixed age groups that included not only children but also adults. In some cases, the authors did not distinguish between the pathology observed in children and adults, making it difficult to determine the relative involvement across age groups. A further complicating factor when interpreting unilateral MB pathology is that asymmetric MBs can occur in the general population, though this appears to generally reflect MB displacement rather than actual atrophy. Good-quality MRIs should help distinguish between these scenarios.

Unfortunately, the size and location of the MBs can often result in poor visualization on MRI, which is exacerbated when scan slices are not sufficiently thin. Furthermore, partial volume
effects can also affect the interpretation of MRI if imaging protocols are not optimized. Together, these are likely to have resulted in MB pathology going undetected. Given the importance of the MBs for memory, accurate identification of MB pathology is necessary to provide appropriate follow-up assessment and support for children and their families. The MBs need to be protected from damage when possible, and thiamine supplementation is an easily implemented measure for critically ill children. A better understanding of the specific pathways that are most likely to result in MB pathology is also needed so more targeted treatments can be developed.

**Disclosure forms** provided by the authors are available with the full text and PDF of this article at www.ajnr.org

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