

Magnetic Resonance Imaging Findings in Bilateral Basal Ganglia Lesions

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Abstract

Introduction: Radiologists may encounter bilaterally symmetrical abnormalities of the basal ganglia on magnetic resonance imaging (MRI), typically in the context of diffuse systemic, toxic or metabolic diseases. A systematic approach and broad knowledge of pathology causing this uncommon group of conditions would be useful. **Materials and Methods:** This review uses illustrative images to highlight metabolic conditions, such as Leigh's syndrome, citrullinaemia, hypoglycaemia or carbon monoxide poisoning, as well as other causes of bilateral basal ganglia lesions such as osmotic myelinolysis, deep cerebral venous thrombosis and Creutzfeldt-Jakob disease. **Results:** Careful assessment of radiological findings outside the basal ganglia, such as involvement of the cortex, white matter, thalamus and pons, together with clinical correlation, may be helpful in narrowing the differential diagnosis, and directing further radiological, biochemical or genetic investigations. Recent advances in MR technology have resulted in newer techniques including diffusion-weighted (DW) MR imaging and MR spectroscopy (MRS); these may be helpful if appropriately used. **Conclusions:** Abnormal MRI findings in the basal ganglia should not be interpreted in isolation. A systematic approach including DW MR imaging, MRS, and a broad knowledge of diffuse systemic, toxic or metabolic diseases is helpful.

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Introduction

The Basal Ganglia

The deep grey matter structures of the basal ganglia comprise the caudate nucleus, putamen and globus pallidus. They form the key components of the extrapyramidal motor system, and receive projections from almost every region of the cerebral cortex, playing a vital role in integrating movement.¹⁻³ The basal ganglia have high energy [adenosine triphosphate (ATP) produced by oxidative phosphorylation within the mitochondria] requirements, increased blood flow and are rich in neurotransmitters and trace metals such as iron, copper and manganese. Hence, they are vulnerable to any systemic disease or generalised process that alters cerebral metabolism, which can lead to selective damage to the basal ganglia. However, damage to the deep grey matter nuclei may be visualised either as basal ganglia lesions in isolation or as part of more generalised brain damage also involving other grey or white matter structures.²

Among the many causes of basal ganglia damage, bilateral

symmetrical lesions typically are caused by diffuse systemic or metabolic conditions.¹⁻³ Often, the cause (for example hypoxic ischaemic encephalopathy in the context of cardiac arrest) is readily evident, but sometimes, the radiologist is faced with situations of bilateral symmetrical lesions in the basal ganglia for initial diagnosis (for example, coma of unknown cause) before the results of relevant investigations are known. The systematic approach to this uncommon group of systemic and metabolic conditions is often challenging, but assessment of all the neuroimaging findings (not merely of the basal ganglia but other features) is an essential component for final diagnosis and sometimes prognosis. The neuroradiologist can thus play an important role in contributing imaging features to the overall clinical, biochemical and genetic picture that makes up an accurate picture of patients with systemic and metabolic disease. This review will describe bilateral basal ganglia lesions from different causes using illustrative examples to highlight neuroimaging and non-imaging features that may be helpful in distinguishing some of them.

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Table 1. Causes of Bilateral Basal Ganglia Abnormalities on Magnetic Resonance Imaging

	Acute	Chronic
Toxic	Carbon monoxide	Manganese
	Cyanide	Methyl benzene (toluene)
	Methanol	
	Disulfiram	
	Hydrogen sulphide	
Metabolic	Hypoxic-Ischemic Injury	Leigh disease
	Hypoglycaemia	Kearns-Sayre syndrome
	Hyperglycaemia	Wilson's disease
	Osmotic myelinolysis	Hypoparathyroidism
	Haemolytic uremic syndrome	Liver disease
		Tay-Sachs disease
		Hallervorden-Spatz disease
		Glutaric acidemia
	Methylmalonic acidemia	
Vascular	Deep cerebral vein thrombosis	
	Hypertensive crisis	
	Cerebral thromboembolism	
Infectious/Transmissible Diseases		Creutzfeldt-Jakob
		Congenital infections
Hereditary/Degenerative		Huntington's disease
		Neurofibromatosis Type 1
Other		Radiation therapy

Aetiology and Clinical Presentation of Bilateral Basal Ganglia Lesions

Several publications and book chapters have classified various conditions causing bilateral basal ganglia lesions according to broad groups including acquired and congenital, paediatric and adult, acute and chronic diseases.¹⁻⁴ A simplified list of possible causes of bilateral basal ganglia abnormalities on magnetic resonance imaging (MRI) is shown in Table 1.

It should also be remembered that although many rare metabolic inborn errors of metabolism are listed as “chronic” conditions, first presentation to MRI may be as an acute unknown diagnosis. There are also exacerbations and relapses, where “acute” changes of abnormal signal and swelling are prominent. Whilst a systematic analytical approach to diagnosis is recommended, no algorithm is simultaneously exhaustive and easy to use. A broad-based background knowledge of pathology (biochemistry and genetics would not hurt either) would be helpful to avoid errors of omission, and assist in the clinically important

tasks of diagnosis, prognosis and genetic counselling.

Typically, diseases of the basal ganglia are characterised by movement disorder associated with damage to the extrapyramidal system. However, not all basal ganglia lesions have been associated with movement abnormalities, and some acute conditions (such as acute deprivation of oxygen or glucose) may be overshadowed by coma or systemic manifestations.¹⁻³ With careful observation of radiologic features, correlation with the clinical presentation and relevant investigations, the differential diagnosis may be whittled to a manageably short list.

MRI Appearance of Basal Ganglia Lesions

The normal basal ganglia are isointense with the grey matter cortex and can be distinguished from the surrounding deep white matter on most pulse sequences. In paediatric patients, immature myelination may result in indistinct intensity differences, but with normal maturation and progressive (physiological) deposition of iron, there is progressive shortening of the T2 signal intensity, resulting in the decrease of signal intensity on T2-weighted images.³

This process occurs first in the globus pallidus followed by the putamen. Although early studies describing bilateral basal ganglia lesions in the pre-MRI era have reported many of the conditions causing basal ganglia hypodensity, atrophy or calcification, this review will focus on the high intensity abnormalities on T2-weighted images.⁴ Most conditions with high signal lesions on T2-weighted images have a corresponding decreased signal on T1-weighted images. Pathologies that result in hyperintense signal on T1-weighted images,⁴ notably Wilson's disease, hepatic failure⁵ and chorea-ballism in hyperglycaemia^{6,7} are covered elsewhere in the literature.⁴

Although systemic or metabolic diseases typically result in bilaterally symmetrical lesions, asymmetrical involvement or unilateral lesions may rarely be seen.³ Some conditions listed as causing basal ganglia lesions may be overshadowed by lesions elsewhere in the brain such as the thalamus, cerebral cortex or white matter. Furthermore, due to bilaterality of lesions, the easy detection by observing asymmetry is lost, and changes in signal intensity may be more subtle. Recent advances in MR technology have resulted in newer techniques of neuroimaging being applied to research and clinical diagnostic imaging. In acute metabolic disease, diffusion-weighted (DW) MR imaging and MR spectroscopy (MRS) may be helpful (see below).

Illustrative Examples

These examples of bilateral basal ganglia hyperintensity on T2-weighted images are taken from a teaching and research database⁸⁻¹⁰ and are not meant to be exhaustive. They serve to illustrate typical cases and highlight associated imaging features that may help in radiological differential diagnosis. They should not be taken to be prototypes or even representative of each category or group, especially the diverse phenotypes of inborn errors of metabolism.

1. Toxic Cause: Carbon Monoxide Poisoning

Carbon monoxide (CO) poisoning is the most common cause of poisoning morbidity and mortality, at least in Europe and North America, often following attempted suicide.¹¹⁻¹⁵ Acute presentations in patients who have inhaled this colourless, odourless gas, formed by incomplete combustion, include cognitive impairment, coma and death; sequelae in survivors include cognitive damage, dementia and Parkinsonian features. Pathological effects of carboxyhaemoglobin on the brain include necrosis, acute demyelination and chronic atrophy, and cases of CO poisoning have been highlighted in many studies of hypoxic-ischaemic encephalopathy, in particular patients with the characteristic syndrome of delayed encephalopathy.¹³⁻¹⁵

On MRI, the globus pallidus is the most common site of bilateral symmetrical abnormality (Fig. 1a).¹⁶ The

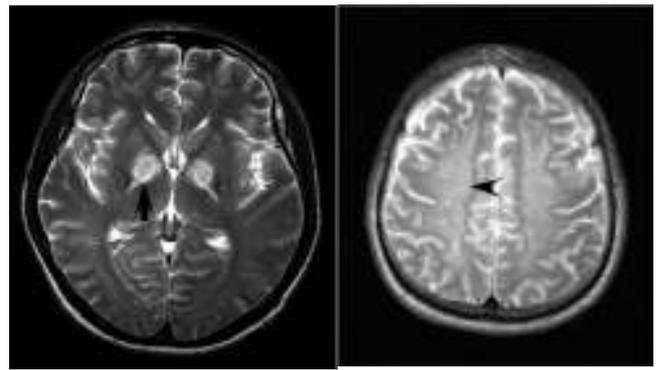


Fig. 1a.

Fig. 1b.

Fig. 1. Carbon monoxide poisoning.

T2-weighted image (a) shows bilaterally symmetrical hyperintensities in the swollen basal ganglia (arrow) and (b) confluent lesions in the frontal deep white matter (arrowhead).

whole basal ganglia can be affected, or the putamen, caudate nucleus, thalamus may be involved in isolation. Haemorrhagic necrosis, best seen on gradient-recalled MRI pulse sequences or on CT, may be detected either acutely or on delayed imaging. The white matter (Fig. 1b) is the second most common site of damage, involving bilaterally symmetrical confluent lesions in the centrum semiovale and periventricular white matter.^{12,17} These may be identified acutely together with globus pallidus lesions, and have also been described in patients with delayed encephalopathy, often without grey matter involvement. The neuroimaging extent correlates with clinical outcomes, and MRI is therefore useful for management and prognosis. Involvement of the cortex, hippocampus and cerebellum is less common. In comatose patients with bilateral symmetrical signal abnormalities of the globus pallidus, together with confluent white matter lesions, especially in the centrum semiovale and periventricular, CO poisoning should be suspected.

2. Vascular Cause: Deep Cerebral Venous Thrombosis (DCVT)

The deep venous system comprises the internal cerebral veins, vein of Galen and straight sinus and it drains the hemispheric white matter, diencephalon and deep nuclei. Like thrombosis of the superficial dural venous sinuses, predisposing factors for DCVT include oral contraceptives, pregnancy and the puerperium.^{18,19} However, in addition to headache and non-specific clinical features, DCVT is characterised by disturbances of consciousness, eye movements, lethargy and long tract signs, and death or poor outcomes.^{18,19} DCVT comprises 3% to 8% of all CVT patients, affecting predominantly women.

The indirect MRI findings in DCVT tend to be dominated by bilateral thalamic lesions, often with involvement of the

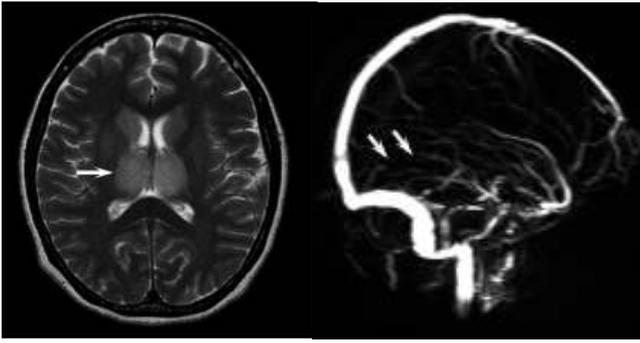


Fig. 2a.

Fig. 2b.

Fig. 2. Deep cerebral venous thrombosis.

T2-weighted image (a) shows bilateral thalamic (arrow) and caudate head hyperintensities. MR venography (b) showing absence of normal flow in the internal cerebral veins, vein of Galen and straight sinus (arrows) and preservation of the superior sagittal and transverse sinuses as well as presence of collateral cortical veins.

basal ganglia (Fig. 2a).²⁰⁻²⁶ Swelling and T2 prolongation may be accompanied by haemorrhagic complication of venous infarction, additional involvement of cerebellum, brainstem or cerebral cortex and hydrocephalus. Rarely, unilateral lesions of the thalamus and basal ganglia have been reported. Direct signs of the thrombosed vein may be subtle on conventional neuroimaging, but MR venography (Fig. 2b) or CT venography is diagnostic. However, these additional pulse sequences or contrast-enhanced venogram studies are not routinely acquired unless the index of suspicion for venous pathology is high.²⁷ Radiologists should recognise the combination of clinical risk factors and bilateral lesions in both the thalamus and basal ganglia (especially if haemorrhagic), and prescribe appropriate venography studies. Although bilateral thalamic arterial infarcts may arise from basilar arterial steno-occlusive disease or embolism, the combined thalamus (posterior arterial circulation) and basal ganglia (anterior circulation) involvement makes arterial stroke unlikely.

3. Transmissible Prion Disease: Creutzfeldt-Jakob Disease (CJD)

Creutzfeldt-Jakob disease is a fatal dementing spongiform neurodegenerative disease.²⁸⁻³¹ It is the most common human transmissible prion disease, and comprises 4 main subtypes: sporadic, familial, iatrogenic and variant CJD. Variant CJD has been linked to bovine spongiform encephalopathy or “mad cow disease” suggesting that isoforms of the prion protein are able to cross the species barrier. Patients with sporadic CJD develop rapidly progressive dementia, myoclonus, and characteristic periodic sharp-wave complexes on electroencephalography. Although MR imaging may be useful in antemortem diagnosis, definitive diagnosis still relies on brain biopsy or autopsy.

Typical findings of CJD include bilateral symmetric abnormalities in the putamen, caudate head as well as involvement of the cerebral cortex (Fig. 3a).³²⁻³⁶ Some reports suggest that axonal transsynaptic spread of the prion agent from the caudate head to the anterior putamen and posteriorly may explain the early asymmetric and late bilateral symmetrical involvement.³⁶ Although cortical lesions are subtle, they are often better detected on DW MR imaging (Fig. 3b).³⁵⁻³⁸ However, it is still unclear why spongiform degeneration should lead to restricted diffusion in CJD. Nevertheless, DW MR imaging lesions correspond to localised EEG changes in the cortex,^{33,38} and correlate with the most severe affected histopathological changes. Hence subtle cortex involvement in addition to bilateral basal ganglia lesions in a patient with dementia and myoclonus would be very suggestive of CJD.

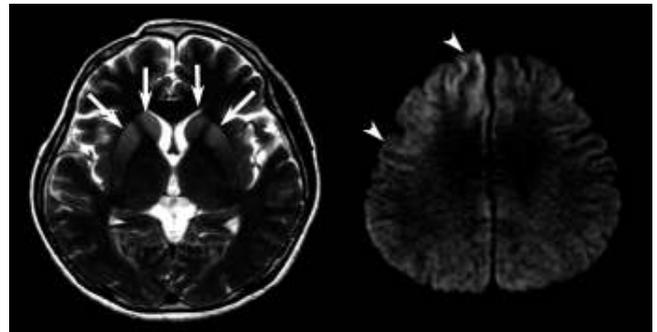


Fig. 3a.

Fig. 3b.

Fig. 3. Creutzfeldt-Jakob disease.

Axial T2-weighted MR image (a) shows abnormal hyperintensity in the caudate head and putamen bilaterally (arrows). Axial diffusion-weighted MR image (b) showing hyperintense lesions in the frontal cortex (arrowheads) in addition to the caudate and putamen lesions.³³

(Reprinted with permission from Lim CC, Tan K, Verma KK, Yin H, Venketasubramanian N. Combined diffusion-weighted and spectroscopic MR imaging in Creutzfeldt-Jakob disease. *Magn Reson Imaging* 2004;22:625-9.)

4. Metabolic Cause: Hypoglycaemia

Brain damage is dependent on the severity and duration of hypoglycaemia, and profound, prolonged hypoglycaemia may lead to seizures, focal neurological deficits, coma and death.³⁹ Patients presenting in hypoglycaemic coma are usually diabetics treated with oral hypoglycaemic agents (such as glibenclamide); rarely non-diabetics with undiagnosed insulinoma of the pancreas or recently in a Singapore outbreak of illegal sexual enhancement drugs tainted by glibenclamide.^{40,41} Glucose is the brain's main energy substrate and severe hypoglycaemia, often inseparable from complications of hypotension or ischaemia, causes neuronal death in the vulnerable grey matter structures of the cortex and basal ganglia.

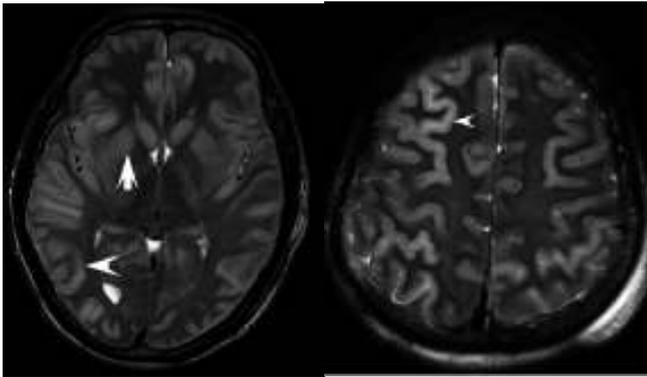


Fig. 4a.

Fig. 4b.

Fig. 4. Hypoglycaemia.

T2-weighted MR images (a) and (b) show bilaterally symmetric confluent hyperintense lesions in the cerebral cortex (arrowheads), posterior hippocampus, and basal ganglia (arrow); the lesions spared the sub-cortical white matter.⁴¹

(Reprinted with permission from Lim CC, Gan R, Chan CL, Tan AW, Khoo JJ, Chia SY, et al. Severe hypoglycaemia associated with an illegal sexual enhancement product adulterated with glibenclamide: MR imaging findings. *Radiology* 2009;250:193-201.)

Studies of MRI in severe hypoglycaemia have reported lesions typically involving the cerebral cortex, hippocampus and basal ganglia bilaterally (Fig. 4). Selective vulnerability of the brain to hypoglycaemic damage may be responsible for characteristic lesion distribution in the temporal lobe cortex, insula and hippocampus basal ganglia and substantia nigra, typically sparing the cerebellum, brainstem and white matter.⁴¹⁻⁴⁶ However, more recently, a different pattern of transient white matter abnormalities DW MR findings, involving the splenium of the corpus callosum, internal capsules and corona radiata, have been reported in patients who later recovered fully without neurological deficit.⁴⁷⁻⁵⁰ Although limited involvement may be a good sign, this pattern of white matter involvement has also been described together with severe grey matter lesions in patients with poor outcome.⁴¹ Involvement of the basal ganglia seems to portend a poor prognosis^{43,44} and in patients with severe hypoglycaemia, diagnosis is usually not difficult in the appropriate clinical context and the presence of widespread cortical lesions.

5. Demyelinating Disease: Osmotic Myelinolysis

Osmotic myelinolysis is a distinct clinical and radiological syndrome originally involving pontine lesions with myelin destruction and axonal necrosis^{51,52} in alcoholics and malnourished individuals with electrolyte imbalance. Initially called pontine myelinolysis, the recognition of bilaterally symmetrical extra-pontine involvement of the basal ganglia, thalami and midbrain has led to the current terminology of osmotic myelinolysis. The syndrome has since been refined to include at-risk populations of

patients with malnutrition, debilitating illnesses such as chronic renal/hepatic failure and syndrome of inappropriate antidiuretic hormone (SIADH). Although the pathogenesis is unclear, the mode of osmotic injury has been linked to aggressive correction of hyponatraemia, with resultant blood brain barrier damage and osmotic vascular injury. Patients may present with spastic quadriparesis, pseudobulbar palsy, altered mental state, coma, locked in syndrome or death.

MRI studies have been reported in the sub-acute or chronic phase of illness, and may reveal involvement of the basal ganglia bilaterally (Fig. 5a).⁵³⁻⁵⁸ The deep white matter may be involved as well, and lesion distribution in osmotic myelinolysis may be dominated by the characteristic “bats-wing” configuration of the pons, spreading out from the median raphe but sparing the descending corticospinal tracts and peripheral pons (Fig. 5b). Reports of DW MR imaging in osmotic myelinolysis have described increased rather than restricted water diffusion, consistent with demyelination, usually without cytotoxic oedema. However, apparent diffusion co-efficient measurements have been heterogeneous, possible reflecting various ages of lesions.^{56,57} Hence, in patients with bilateral basal ganglia plus pontine lesions that are not restricted on DW MR imaging, osmotic myelinolysis should be suspected.

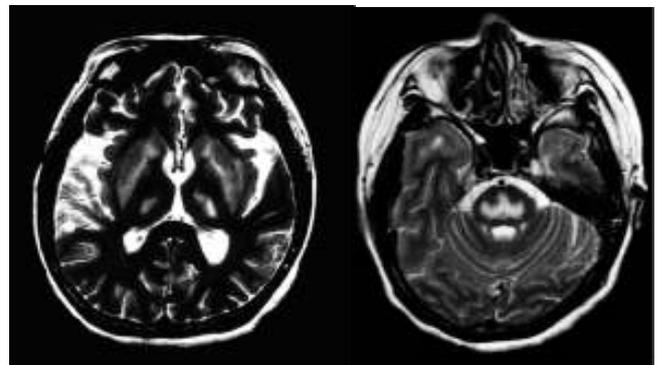


Fig. 5a.

Fig. 5b.

Fig. 5. Osmotic myelinolysis.

Axial T2-weighted images (a) show bilateral symmetrical high intensity in the caudate heads, basal ganglia and thalami and (b) the characteristic “bats-wing” appearance of central pontine myelinolysis.⁵⁷

(Reprinted with permission from Chua GC, Sitoh YY, Lim CC, Chua HC, Ng PY. MRI findings in osmotic myelinolysis. *Clin Radiol* 2002;57:800-6.)

6. Inborn Error of Metabolism: Citrullinaemia

Citrullinaemia is an inborn error of urea cycle metabolism: deficiency of argininosuccinate synthetase in the liver results in abnormal accumulation of citrulline and ammonia metabolites in the plasma, leading to the failure to detoxify the body’s nitrogenous waste.⁵⁹⁻⁶² Accumulation of ammonia can lead to encephalopathy, coma and death. Although most patients with fatal inborn errors of urea cycle

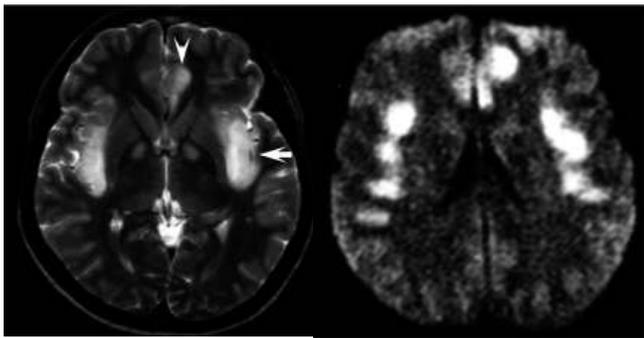


Fig. 6a.

Fig. 6b.

Fig. 6. Citrullinaemia.

T2-weighted image (a) and DW MR image (b) show high signal intensity in the left cingulate gyrus (arrowhead) and insula (arrow) bilaterally. Note the hyperintensity in the globus pallidus bilaterally.⁶³ (Reprinted with permission from Au WL, Lim TC, Seow DC, Koh PL, Loh NK, Lim MS, et al. Serial diffusion-weighted magnetic resonance imaging in adult-onset citrullinaemia. *J Neurol Sci* 2003;209:101-4.)

metabolism present to clinical attention early in the neonatal period and rarely survive to adulthood, a few uncommon, less severe, late onset urea enzyme disorders including ornithine transcarbamylase deficiency, carbamylphosphate synthetase deficiency, argininosuccinate lyase deficiency and argininosuccinate synthetase deficiency (citrullinemia) may present in adulthood with intermittent episodes of hyperammonaemic encephalopathy.^{59,61} Unlike Type I neonatal citrullinaemia, patients with Type II citrullinaemia are rarely seen outside Japan, and patients presenting with elevated serum ammonia with non-specific neuropsychiatric symptoms, lethargy, postprandial cognitive disturbance, seizures, delusion and hallucinations may experience delays in diagnosis and life-saving treatment. Other causes of hyperammonaemia besides inherited urea cycle defects include acute and chronic liver failure.

DW MR imaging showing corresponding reduced apparent diffusion co-efficient consistent with cytotoxic damage has also been reported.⁶³⁻⁶⁵ MRI findings in hyperammonaemia including adult onset citrullinaemia include striking involvement of the cingulate gyrus and the insular cortex bilaterally and symmetrically, together with basal ganglia (Fig. 6) and the depths of the cortical sulci,⁶²⁻⁶⁶ and this pattern of abnormalities should trigger a biochemical survey for serum ammonia and hepatic function test.

7. Mitochondrial Disease: Leigh's Syndrome

Subacute necrotising encephalomyelopathy or Leigh's syndrome is an inherited autosomal recessive defect in the enzyme pathway for respiratory metabolism. Patients with mutations in mitochondrial DNA or in nuclear DNA, suffer from selective damage to the basal ganglia, which

are rich in mitochondria and energy metabolism. Infantile (less than 2 years) and juvenile forms have variable onset of psychomotor regression, weakness, seizures, dystonia and cerebellar dysfunction, leading to death from progressive respiratory failure.^{67,68}

MR imaging typically shows bilateral areas of high signal intensity on T2-weighted images in the basal ganglia (Fig. 7a), periventricular white matter, corpus callosum, brainstem and spinal cord.^{69,70} Although commonly categorised as a chronic metabolic disease, Leigh's is characterised by episodic symptomatic exacerbations, and neuroradiologists may find dynamic resolution of acute abnormalities and development of new lesions on follow-up. Proton MR spectroscopy has demonstrated elevated brain lactate levels in the active lesions in the basal ganglia (Fig. 7b),⁷⁰ and this finding may be a helpful sign supporting the diagnosis in young children presenting acutely for the first time. A combination of typical MRI features, elevated MR spectroscopic, serum and CSF lactate may be helpful for the diagnosis of probable Leigh's syndrome and trigger appropriate genetic testing and counselling.

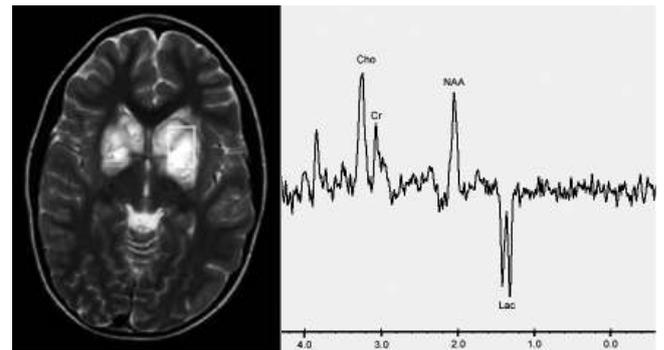


Fig. 7a.

Fig. 7b.

Fig. 7. Leigh's syndrome.

T2-weighted MR image (a) shows bilaterally symmetrical hyperintensities in the basal ganglia and putamen. Proton MR spectroscopy (b) demonstrates abnormal levels of lactate (Lac), inverted bifid peak at echo time of 144 msec in the affected basal ganglia lesion with decreased N-acetyl aspartate (NAA), creatine (Cr) and choline (Cho).

Differentiating Features and Diagnostic Approach

Among the many causes of basal ganglia damage, bilateral symmetrical lesions are typically part of more generalised brain damage involving other structures. The cause may be diffuse systemic toxic or metabolic conditions such as Leigh's syndrome, citrullinaemia, hypoglycaemia or carbon monoxide poisoning, but may also be due to vascular DCVT, prion-associated CJD, or osmotic myelinolysis. A systematic approach to uncommon but characteristic finding of T2 prolongation in the basal ganglia bilaterally may be challenging, but complete assessment of all the radiological features, including bilateral confluent white matter lesions,

cortical or insula lesions, involvement of the thalamus or pons may be helpful in differential diagnosis. Correlation with results of clinical and investigational tests within multi-disciplinary team conferences⁷¹ can also be useful in narrowing and categorising the differential diagnosis and directing further radiological or other investigations. Advanced MRI pulse sequences such as venography and spectroscopy, but above all, DW MR imaging, may be helpful when appropriately used.

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