Idiopathic Inflammatory Demyelinating Diseases of the Brainstem

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SUMMARY

• INTRODUCTION
• CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM
• BRAINSTEM INVOLVEMENT IN MULTIPLE SCLEROSIS
• CONTRIBUTION OF BRAINSTEM LESIONS TO THE MRI DIAGNOSTIC CRITERIA OF MULTIPLE SCLEROSIS
• ROLE OF INFRATENTORIAL LESIONS IN THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS
• BRAINSTEM INVOLVEMENT IN DEVIC’s NEUROMYELITIS OPTICA
• BRAINSTEM INVOLVEMENT IN ACUTE DEMYELINATING ENCEPHALOMYELITIS AND BICKERSTAFF ENCEPHALITIS
• CONCLUSIONS
SUMMARY

- INTRODUCTION
- CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM
- BRAINSTEM INVOLVEMENT IN MULTIPLE SCLEROSIS
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- BRAINSTEM INVOLVEMENT IN DEVIC’s NEUROMYELITIS OPTICA
- BRAINSTEM INVOLVEMENT IN ACUTE DEMYELINATING ENCEPHALOMYELITIS AND BICKERSTAFF ENCEPHALITIS
- CONCLUSIONS
INTRODUCTION

Idiopathic inflammatory-demyelinating diseases (IIDD’s) represent a broad spectrum of central nervous system (CNS) disorders that can be differentiated on the basis of severity, clinical course, and lesion distribution, as well as by imaging, laboratory and pathological findings. The spectrum includes monophasic, multiphasic, and progressive disorders, ranging from highly localized forms to multifocal or diffuse variants.

All forms of IIDDs may affect the brainstem, usually together with other areas of the CNS, and only rarely in isolation. This exhibit reviews the clinical and imaging features of brainstem involvement in the different IIDD’s.
Idiopathic inflammatory demyelinating diseases of the CNS

**Severity**

**Fulminant IIDDs**
- Marburg disease
- Schilder disease
- Balo concentric sclerosis
- ADEM

**Restricted forms of IIDDs**
- Devic NMO
- Relapsing optic neuritis
- Relapsing transverse myelitis

**Pseudotumoral forms**

**Recurrent forms of MS**
- Optic neuritis
- Brainstem syndrome
- Acute transverse myelitis

**Benign MS**

**Monosymptomatic IIDDs**
- Optic neuritis
- Brainstem syndrome
- Acute transverse myelitis

**Primary progressive MS**

**Fulminant IIDDs**
- Chronicity
SUMMARY

• INTRODUCTION
• CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM
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• CONTRIBUTION OF BRAINSTEM LESIONS TO THE MRI DIAGNOSTIC CRITERIA OF MULTIPLE SCLEROSIS
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• BRAINSTEM INVOLVEMENT IN DEVIC’s NEUROMYELITIS OPTICA
• BRAINSTEM INVOLVEMENT IN ACUTE DEMYELINATING ENCEPHALOMYELITIS AND BICKERSAFF ENCEPHALITIS
• CONCLUSIONS
Multiple Sclerosis (MS) is the most representative IIDD; arguably, all other IIDDs can be considered as variants of MS.

Relapsing forms of MS account for 85% of all cases. This clinical form typically presents as an acute clinically isolated syndrome (CIS) attributable to monofocal or multifocal CNS demyelinating lesions that usually affect the optic nerve (optic neuritis), spinal cord (acute transverse myelitis), brainstem (typically an internuclear ophthalmoparesis), or cerebellum (clumsiness and gait ataxia).
Typical presentations of **CIS** of the **brainstem** include:
- bilateral internuclear ophthalmoplegia
- sixth nerve palsy
- facial numbness

Less common presentations include:
- unilateral internuclear ophthalmoplegia
- facial palsy
- facial myokymia
- deafness, one-and-a-half syndrome
- trigeminal neuralgia

Atypical clinical presentations not expected in MS include:
- complete external ophthalmoplegia
- vertical gaze palsies
- vascular territory syndromes
- third nerve palsy
- progressive trigeminal sensory neuropathy
Brainstem syndromes suggestive of inflammatory demyelination are often the first clinical manifestation of MS, although they may also remain a monophasic disease. In these patients, brain MR plays an essential role with two different objectives.

1. To demonstrate the symptomatic lesion and to rule out a non-demyelinating lesion as the cause of the symptoms.

Clinically isolated syndrome of the brainstem (internuclear ophthalmoplegia) in two different young patients. Sagittal fast-FLAIR MR image shows the symptomatic demyelinating lesion located in the floor of the IV ventricle in one patient (left) and a diffuse brainstem glioma in the other (right).
2. To search for subclinical lesions in the CNS, as this will predict the risk of conversion to clinically definite MS.

82% of patients with a CIS and brain lesions consistent with demyelination on T2WI (75% of patients with a brainstem CIS) develop clinically definite MS over the subsequent 20 years, compared to 21% of those with normal findings (see diagram next slide).

The risk of conversion to MS is increased by the presence of oligoclonal bands in CSF.

Fisniku L et al. *Brain* 2008
Brain MR positive 75%

Median time to conversion 2 years

Clinical threshold

Brainstem CIS

82%

20 years CDMS

Fisniku L et al. Brain 2008
Symptomatic brainstem lesions in CIS patients show a tendency to involve the peripheral areas of the pons, including the floor of the IV ventricle, or the middle cerebellar peduncles, with relative sparing of the central white matter. Lesions vary in size, although pseudotumoral lesions are rare.
SUMMARY

• INTRODUCTION
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• CONTRIBUTION OF BRAINSTEM LESIONS TO THE MRI DIAGNOSTIC CRITERIA OF MULTIPLE SCLEROSIS
• ROLE OF INFRATENTORIAL LESIONS IN THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS
• BRAINSTEM INVOLVEMENT IN DEVIC’s NEUROMYELITIS OPTICA
• BRAINSTEM INVOLVEMENT IN ACUTE DEMYELINATING ENCEPHALOMYELITIS AND BICKERSTAFF ENCEPHALITIS
• CONCLUSIONS
MS frequently affects the brainstem, leading to acute clinical syndromes, such as trigeminal neuralgia and internuclear ophthalmoplegia. Later on, chronic damage to the brainstem causes chronic disabling symptoms, such as oculomotor disturbances. Acute symptomatic lesions appear as well-defined, hyperintense, focal lesions that enhance with contrast administration on T1W images.
Most brainstem lesions are contiguous with the cistern or ventricles and range from large confluent patches to solitary, well-delineated, paramedian lesions or discrete "linings" of the CSF border zones. Predilection for these areas helps identify MS plaques and differentiate them from focal areas of ischemic demyelination and infarction, which normally involve the central pontine white matter.

The preferred areas of involvement are the floor of the fourth ventricle, the middle cerebellar peduncles, and the surface of the pons.
Medulla oblongata MS plaques may have a uni- or bilateral paramedian location, which could be explained by the pattern of venous drainage in the ventral medulla.
Brainstem lesion volume in MS patients is higher in the chronic progressive forms than in the benign and relapsing-remitting forms of the disease. Confluent lesions are only found in the chronic progressive forms.

Observe the different lesion extension in patients with MS, depending on the clinical phenotype of the disease.
Infrequently, MS lesions of the brainstem may present as a large focal lesion that can cause severe acute symptoms requiring aggressive anti-inflammatory treatment.

MS patient who presented a severe brainstem relapse. Note the development of a large MS plaque in the pons. Steroids were ineffective and the patient required plasma exchange.
Since infratentorial lesions are important for diagnosing MS and predicting long-term disability, various sequences have been evaluated to increase the sensitivity of MRI in detecting posterior fossa lesions.

At standard field strengths (1.5T), proton-density and T2W (turbo) spin echo (SE) are more sensitive than FLAIR in detecting infratentorial lesions.

Axial T2 (left) PD (middle) and FLAIR (right) MR images in a patient with MS. Note the better depiction of MS plaques on both T2 and PD compared to FLAIR images.
At 3 T imaging, there are no significant differences in sensitivity between PD/T2 and FLAIR sequences for detection infratentorial lesions.

Wattjes MP et al. *Eur Radiol* 2006

Axial T2 (left) and FLAIR (right) MR images at 3.0 T in a patient with MS. Lesions are slightly better depicted with FLAIR compared to T2 images.
At 3 T, double inversion recovery (DIR) sequences seem to have higher overall sensitivity for detecting focal MS lesions in the infratentorial regions than the T2 TSE and FLAIR.

Axial 3T 3D DIR (upper), 2D FLAIR (middle), and T2W TSE (lower) MR images. Multiple small lesions in the brainstem (left side) and superior cerebellar peduncle are easily detected on the DIR sequence, while very difficult to identify on FLAIR and T2 TSE sequences.
MULTIPLE SCLEROSIS. BLACK HOLES

Approximately 10% to 20% of T2 hyperintense MS plaques are also visible on T1W images as areas of low signal intensity compared with normal appearing white matter. These so-called “T1 black holes” correlate pathologically with areas of severe demyelination and axonal loss, indicating areas of irreversible tissue damage.

van Walderveen et al. Neurology 1998
Black holes are more frequent in patients with progressive disease than in those with relapsing-remitting disease, and more frequent in the supratentorial white matter as compared with the brainstem and cerebellar white matter, in which they are very rare.

Gass et al. showed that 40% of T2 lesions in the cerebral white matter were hypointense on T1W images (black holes), in comparison to only 0.5% in the brainstem.

Gass et al. *Neurology* 1998

Axial T2W (*upper row*) and T1W (*lower row*) brain MR images obtained in a patient with a progressive form of MS. Observe how most of T2 supratentorial lesions are hypointense on T1W images, while T2 brainstem lesions are isointense.
MULTIPLE SCLEROSIS
BRAINSTEM LESIONS: BLACK HOLES

The lack of T1 black holes might be due to the tissue architecture of the brainstem, in which fibers run predominantly in parallel. This feature prevents interstitial water accumulation and thus the formation of a T1 black hole in chronic lesions with severe demyelination and axonal loss, which instead will produce atrophy.

Chronic black holes involving the brainstem. Axial T2W (upper row) and T1W (lower row) brain MR images obtained in a patient with a progressive form of MS. Observe the diffuse involvement of the pons and the low signal intensity of the lesions on T1W images.
The cisternal portion of the trigeminal and oculomotor nerves is thickened and enhanced (often bilaterally) in almost 3% of MS patients. In most cases, this abnormality is not associated with trigeminal neuralgia and only a minority of patients have painless and paraesthesias in the corresponding V3 distribution.

Da Silva et al. *Mult Scler* 2005

T1W axial images performed before (*upper row*) and after gadolinium injection (*lower row*) in a patient with MS. Observe the marked bilateral enhancement and thickening of the cisternal segments of the Vth and IIIth nerves.
The presence of at least 2 infratentorial lesions is a strong predictor of disability progression for patients with initial findings suggestive of MS. Therefore, the number of brainstem and cerebellar lesions may help identify patients at high risk for earlier occurrence of clinically relevant disability.

Percentage of patients with Expanded Disability Status Scale (EDSS) less than 3 at follow-up after dichotomizing for infratentorial lesions (2 vs 2 infratentorial lesions).

Minneboo et al. Arch Neurol 2004
A high percentage of MS lesions are found in the brainstem. However, various other pathologies, particularly cerebrovascular diseases, may produce lesions with features similar to infratentorial MS. Nevertheless, the MR imaging pattern of brain MS is usually relatively specific when age, clinical information, and the full range of MR imaging abnormalities (including lesion number, distribution, size, shape, associated volume changes, and contrast enhancement) are taken into consideration.
The classical wedge shape of pontine infarction may suggest ischemia. The ischemic origin is best shown using diffusion-weighted MRI. A reduced apparent diffusion coefficient indicates cytotoxic cell swelling, an early event in the development of ischemic tissue injury.

**MRI of acute pontine infarction.** T2W MRI (left) shows a lesion can be seen on the left side of the pons. It is well delineated on diffusion-weighted MRI (center) and the corresponding hypointensity on the apparent diffusion coefficient map (right) is compatible with cytotoxic edema and indicates an early phase of infarction.
Acute demyelinating brainstem lesions are commonly identified as well-defined foci of high signal intensity at T2, often accompanied by contrast enhancement. The concomitant presence of MS-type supratentorial white matter lesions is the key MR diagnostic feature.

**MRI of acute brainstem CIS.** On T2W MRI (left) a lesion is seen on the left side of the pons. The lesion is well-delineated, shows peripheral contrast uptake (center), and is associated with multiple focal periven-tricular lesions of the type seen in MS.
MS. BRAINSTEM LESIONS: DIFFERENTIAL DIAGNOSIS

Small-vessel disease vs multiple sclerosis

MS pontine lesions are contiguous with the CSF spaces of the cisterns or ventricles (floor of the IV\textsuperscript{th} ventricle), likely due to the pontine pattern of venous drainage, while small-vessel disease lesions usually involve the central white matter, which is particularly vulnerable to small-vessel disease and hypoperfusion.
SUMMARY

• INTRODUCTION
• CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM
• BRAINSTEM INVOLVEMENT IN MULTIPLE SCLEROSIS
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• ROLE OF INFRATENTORIAL LESIONS IN THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS
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• BRAINSTEM INVOLVEMENT IN ACUTE DEMYELINATING ENCEPHALOMYELITIS AND BICKERSTAFF ENCEPHALITIS
• CONCLUSIONS
CONTRIBUTION OF BRAINSTEM LESIONS TO THE DIAGNOSTIC CRITERIA OF MS

All the diagnostic criteria for establishing the diagnosis of MS proposed in the last 50 years are based on three main principles:

1) demonstration of disease dissemination in space (DIS)
2) demonstration of disease dissemination in time (DIT)
3) reasonable exclusion of alternative explanations for the clinical presentation.
MRI has high sensitivity for detecting MS plaques throughout the brain and spinal cord. However, comparable MRI abnormalities are seen in many other diseases and even in healthy subjects; hence, criteria have been developed to classify whether MRI findings are suggestive of MS. Most of these criteria consider the posterior fossa (brainstem and cerebellum) one of the three characteristic regions (together with periventricular and juxtacortical) for multiple sclerosis lesions.
MS DIAGNOSTIC CRITERIA

Fazekas criteria

≥ 3 T2 lesions, with at least two of the following characteristics:
✓ size > 5 mm
✓ infratentorial location
✓ abutting the ventricular body

These criteria were evaluated retrospectively in established MS and other disorders and showed both high sensitivity and high specificity for MS. However, they performed less well in predicting conversion to clinically definite MS when applied prospectively in CIS patients.

Fazekas et al. Neurology 1988
The modified Barkhof criteria require at least 3 of the following 4 features:

- Gd-enhancing lesion (at least 1) or 9 hyperintense T2 lesions if Gd-enhancing lesions are not present
- Juxtacortical location (at least 1)
- Periventricular location (at least 3)
- Infratentorial location (at least 1)

Compared to previous criteria, this criteria achieve a higher diagnostic accuracy and a better balance between sensitivity and specificity to predict conversion from CIS to clinically definitive MS.

In 2006, Swanton et al., proposed new MRI criteria for MS that require the detection of one or more subclinical T2 lesion(s) in at least two of four locations considered characteristic for MS in the McDonald criteria: juxtacortical, periventricular, infratentorial, and spinal cord.

Compared with the Barkhof criteria, the Swanton criteria are similarly (highly) specific for predicting conversion from CIS to clinically definitive MS, more sensitive, and probably easier to remember and to apply in clinical practice.

Swanton et al. J Neurol Neurosurg Psychiatry 2006
Swanton et al. Lancet Neurol 2007
SUMMARY

• INTRODUCTION
• CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM
• BRAINSTEM INVOLVEMENT IN MULTIPLE SCLEROSIS
• CONTRIBUTION OF BRAINSTEM LESIONS TO THE MRI DIAGNOSTIC CRITERIA OF MULTIPLE SCLEROSIS
• ROLE OF INFRATENTORIAL LESIONS IN THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS
• BRAINSTEM INVOLVEMENT IN DEVIC’S NEUROMYELITIS OPTICA
• BRAINSTEM INVOLVEMENT IN ACUTE DEMYELINATING ENCEPHALOMYELITIS AND BICKERSTAFF ENCEPHALITIS
• CONCLUSIONS
Devic’s neuromyelitis optica (NMO) is an uncommon and topographically restricted form of IIDD that is considered a distinct disease rather than a variant of MS. NMO is characterized by severe unilateral or bilateral optic neuritis and complete transverse myelitis, which occur simultaneously or sequentially within a varying period of time (weeks or years), without clinical involvement of other CNS regions.

Pittock et al. Sem Neurol 2008
Wingerchuk et al. Lancet Neurol 2008
NMO first presents are severe unilateral or bilateral optic neuritis, acute myelitis, or a combination of these symptoms. Attacks of complete transverse myelitis occur with severe bilateral motor deficits, sensory level and bowel and bladder dysfunction, pain and significant residual neurological injury. NMO attacks are generally more severe than in MS. Approximately 85% of patients have a relapsing course with severe acute exacerbations and poor recovery, accumulating increasing neurological impairment and a high risk of respiratory failure and death due to cervical myelitis.
Spinal cord MRI cord shows extensive cervical or thoracic tumefactive myelitis involving more than three vertebral segments on sagittal and much of the cross-section on axial T2W images, which sometimes enhances with gadolinium for several months. Unilateral or bilateral optic nerve enhancement may be seen during acute optic neuritis. In contrast to MS, white matter lesions are often absent.
Asymptomatic brain lesions are common in NMO, but symptomatic brain lesions do not rule out NMO. Brain abnormalities are found in 60% of NMO patients at MRI. Most lesions are nonspecific, but some are similar to MS. Children with NMO sometimes have diencephalic (hypothalamic), brainstem, or cerebral hemispheric lesions, which should be considered atypical for MS.

Sagittal T2W cervical cord (left), sagittal DIR brain (middle), and axial T2W brain (right) MR images in a patient who met the diagnostic criteria of NMO. In addition to extensive cervical cord myelitis and involvement of the optic chiasm (arrow), brain MR shows peripheral involvement of the brainstem.
Although most brain lesions in patients with NMO are nonspecific, lesions in the brainstem and hypothalamus are relatively characteristic for NMO. Characteristic MRI brain lesions occur adjacent to the ventricular system at any level but occur more commonly around the III\textsuperscript{th} and IV\textsuperscript{th} ventricle and the aqueduct of Sylvius than around the lateral ventricles. The distribution of these lesions mirrors the periven- tricular and hypothalamic localization of aquaporin 4, a water channel located on the foot process of the astrocyte, considered the target antigen of NMO.

Red dots indicate areas of high aquaporin 4 expression in the peri-ependymal regions, which correspond to regions of MRI abnormalities.

Pittock et al. *Arch Neurol* 2006

Representative MRIs show brain lesions in periependymal regions with high aquaporin 4 expression. T2 signal abnormalities are seen around the III ventricle with extension into the hypothalamus (left) and in tissue surrounding the IV ventricle with extension into cerebellar peduncles (right).
SUMMARY

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• CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM
• BRAINSTEM INVOLVEMENT IN MULTIPLE SCLEROSIS
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• ROLE OF INFRATENTORIAL LESIONS IN THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS
• BRAINSTEM INVOLVEMENT IN DEVIC’S NEUROMYELITIS OPTICA
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• CONCLUSIONS
Acute disseminated encephalomyelitis (ADEM) is a severe acute demyelinating disease of the CNS, usually triggered by an inflammatory response to viral infections or vaccinations. ADEM affects children more often and is usually monophasic. Children with ADEM often present frequently with signs and symptoms of brainstem/cerebellar dysfunction (ataxia, oculo-motor disturbance and dysarthria). These signs and symptoms are less common but not rare in adults; some authors have reported prevalences as high as 62%.

Axial T2W brain MR images in a young patient with ADEM. Note the bilateral subcortical hemispheric lesions associated with a large lesion involving the brainstem.

Krupp et al. Neurology 2007
Tenembaum et al. Neurology 2007
Bickerstaff encephalitis is a rare form of acute 
brainstem 
syndrome affecting adolescents and young adults. It is 
considered a subgroup of ADEM in which inflammation appears 
to be confined to the brainstem. 
This form of ADEM is characterized by the subacute (day to 
several weeks) development of brainstem dysfunction, 
including ophthalmoplegia, facial palsies, sensory loss, 
dysarthria, deafness and ataxia. 
Bickerstaff encephalitis is associated with mild fever and 
usually with an increased white cell count in the CSF. A 
prodromal illness of malaise and headache of several months is 
characteristic.
Bickerstaff encephalitis. Initial brain MR imaging shows an extensive brainstem lesion (upper row) that fully resolved in a follow-up study obtained 8 months later (lower row).

MRI usually shows an extensive high-signal intensity lesion on T2W images involving the midbrain, the pons, and sometimes the thalamus. The clinical outcome is good and parallels resolution of the MRI lesions. The pathogenesis of Bickerstaff encephalitis is uncertain; however, the absence of CSF oligoclonal bands and resolution of the clinical symptoms and MRI lesions suggest an inflammatory origin and make demyelination unlikely.
SUMMARY

• INTRODUCTION
• CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM
• BRAINSTEM INVOLVEMENT IN MULTIPLE SCLEROSIS
• CONTRIBUTION OF BRAINSTEM LESIONS TO THE MRI DIAGNOSTIC CRITERIA OF MULTIPLE SCLEROSIS
• ROLE OF INFRATENTORIAL LESIONS IN THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS
• BRAINSTEM INVOLVEMENT IN DEVIC’s NEUROMYELITIS OPTICA
• BRAINSTEM INVOLVEMENT IN ACUTE DEMYELINATING ENCEPHALOMYELITIS AND BICKERSTAFF ENCEPHALITIS
• CONCLUSIONS
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• The brainstem may be involved in different forms of idiopathic inflammatory demyelinating diseases (IIDD’s).

• Brainstem syndromes are frequently the first clinical manifestation of MS.

• Brainstem MR lesions are accepted as one of the criteria used to establish the diagnosis of MS and have an important impact on the development of disability.
CONCLUSIONS

• In MS patients, brainstem lesions have a relatively characteristic topography that helps to differentiate them from focal areas of ischemic demyelination.

• The brainstem can also be involved in other inflammatory-demyelinating diseases, such as ADEM and NMO.

• Bickerstaff encephalitis is a rare form of acute brainstem syndrome considered a subgroup of ADEM in which inflammation appears to be confined to the brainstem.