THE BRAIN OVER THE JOINTS: MRI brain findings in Rheumatoid Arthritis

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Learning objectives

Joints are the main target of rheumatoid arthritis (RA), however RA is a systemic inflammatory process that can also affect central nervous system (CNS). The aim of this study is to provide a comprehensive spectrum of intracranial MRI findings in RA, pointing out their relationship with systemic RA inflammatory activity and neurological symptoms.
Background

Neurologic RA manifestations are associated with significant morbidity and may be easily overlooked or incorrectly assigned to peripheral arthritis. Their aware framing with MRI is mandatory to direct a prompt therapeutic management.
Intracranial RA manifestations may arise from the systemic inflammatory process itself (1) or from drugs used for treatment (2) (Fig. 1-Table 1).

(1) PRIMARY MANIFESTATIONS

(1.1) Rheumatoid vasculitis is a necrotizing vasculitis of small and medium-sized vessels, with a predilection for skin and the peripheral nervous system. The involvement of cerebral vessels in RA (cerebral vasculitis - CV) can present as part of a systemic manifestation of vasculitis, or, less frequently, with isolated involvement of the brain. It appears most commonly in patients with long-standing seropositive RA and with high RF titers. CV involves both parenchymal and meningeal vessels, but tends to spare large vessels, such as the middle cerebral artery. The exact mechanisms involved in the development of RA-associated cerebral vasculitis have not been identified. It seems to be mediated by IgG rheumatoid factor (RF), immune complexes, and complement activation (particularly C3 and C4). The most common presentation is an insidious non-localising encephalopathy or a chronically progressive headache, focal neurological manifestations like transient ischaemic attack (TIA) and seizures. Microscopically, all vascular layers are infiltrated by mononuclear fibrinoid necrosis and intima proliferation. Imaging signs of CV may be direct (vessel wall thickening with contrast enhancement) or indirect (cerebral perfusion deficits, ischemic brain lesions, intracerebral or subarachnoid hemorrhage, and vascular stenosis) (Table 2). Multiple bilateral infarcts of different ages are suggestive of CV, especially if the lesions are located randomly in various vascular territories without a typical embolic pattern. Breakdown of small vessels can also lead to chronic petechial haemorrhages, best seen on T2* gradient-echo sequences. Magnetic resonance angiography (MRA) has only recently become capable of uncovering the finer vascular abnormalities and the intramural vascular inflammation underway in the vessel wall. There is diffuse segmental arterial wall narrowing, followed by post-stenotic dilation, an appearance referred to as 'beading' or "string-of-beads". 'Beading' may be smooth or irregular, and classically does not cluster around sites of vessel bifurcation, despite the presence of atherosclerotic abnormalities. MR abnormal leptomeningeal enhancement is typical of rheumatoid CV and partly reflects cortical acute ischaemic changes due to the small vessel vasculitis, involving meningeal vessels (Fig. 2).

(1.2) Rheumatoid meningitis, is also rare, but more of a familiar form of central nervous system (CNS) involvement of RA. On the basis of non-specific clinical, imaging and laboratory findings, the diagnosis, short of doing a brain biopsy, is made by exclusion, and requires correlation of clinical-laboratory data and radiological findings. Clinically, it may cause seizures, cranial nerve dysfunction, impairment of vigilance and consciousness, behavioral changes, headache, meningeal syndrome, and hemiparesis.
CSF laboratory analysis is usually abnormal, showing an elevated protein level with occasional pleocytosis and a depressed glucose level; serologic results are positive for rheumatoid factors and for more specific anti-CCP antibodies. MR imaging findings in rheumatoid meningitis include meningeal thickening and contrast-enhancement involving, to a variable extent, leptomeninges and/or pachymeninges, with a linear and/or nodular pattern. Fibrinoid material and debris might be found in the subarachnoid space, resulting in abnormal signal intensity on T1- and T2-W images, especially on FLAIR. There is also high signal intensity on DW images with corresponding diffusion restriction on ADC maps. Restricted diffusion in the subarachnoid space has been described in the presence of purulent leptomeningeal exudates, although it might also reflect cortical acute ischemic changes due to the small vessel vasculitis, that involves meningeal vessels. Pathological examination reveals leptomeningeal inflammatory changes with necrosis, consistent with meningeal localization of rheumatoid arthritis. The diffusely increased T2-signal observed in the adjacent brain parenchyma, involving cortex and sub-cortical white matter, was most likely consistent with inflammatory reactive edema; focal parenchymal lesions, especially visible in a cortical distribution, reflect vasculitis related to a lymphoplasmyacytic infiltrate in the parenchymal vessel walls (Fig. 3-4).

(1.3) Documented CNS manifestation of RA includes choroid plexus infiltration. This is an early and non-specific sign of CNS involvement in inflammatory disorders. The choroid plexus plays a critical role in the communication between the immune system and CNS. Choroid plexus enlargement and infiltration suggest disruption of the blood-brain barrier (BBB) secondary to active inflammation.

(1.4) RA-CNS findings related to atlantoaxial subluxation (AAS) are multiple cerebral and cerebellar infarcts caused by positional occlusion of the vertebral artery and Chiari malformation due to progressive basilar invagination. AAS is common in patients with progressive RA due to involvement of atlantoaxial joints in the autoimmune inflammatory process. MRI is particularly valuable in the assessment of the pannus producing cord compression, and in the visualization of the spinal cord and bone. Four synovial articulations occur between the atlas and axis and are involved in RA synovitis: two lateral atlantoaxial joints, one on each side (between the inferior facet of the lateral mass of the atlas and the superior facet of the axis); and two median synovial joints, one minor anterior (between the anterior arch of the atlas and the odontoid process of the axis) and a second larger posterior (that lies between the cartilage-covered anterior surface of the transverse ligament of the atlas and the grooved posterior surface of the odontoid process). AAS can occur anteriorly, posteriorly, vertically, laterally and/or rotationally.

(1.4.1) Positional occlusion of the vertebral artery

Any form of atlantoaxial instability and subluxation can produce increased contortion and fragility of the vertebral artery (VA) as it passes around the intervertebral foramina of C1 and C2, particularly because the vertebral artery passes oblique to the C1 foramen...
and this condition can induce VA narrowing and compression. With repeated or continual occurrence, thrombus formation can be induced and lead to brain infarction. In vertical AAS in particular, with displacement of the odontoid process into the foramen magnum, narrowing and constriction of the vertebral artery in an hourglass fashion between the tip of the odontoid process and the lip of the foramen magnum can occur. Clinical manifestations are related to the sites of the lesions and include cerebellar signs such as double vision and cerebellar ataxia. MRI findings are bilateral infarcts at different stages, that involve vertebrobasilar territories (bilateral cerebellum, occipital lobes andpons). MR imaging can also document a pannus eroding the odontoid peg, superior migration of the odontoid process, or vertical AAS; this finding is better assessed by the Sakaguchi-Kauppi method (Fig. 5), with the detection of a fallen atlas around the axis (categorized into grades II, III, IV), while McRae and McGregor’s lines may both be less sensitive if the apex of the odontoid is eroded. Insufficiency of the vertebral artery circulation must therefore be suspected, in RA patients with multiple cerebral and cerebellar infarctions in the territory of the vertebrobasilar artery (Fig. 6). Finally, it is necessary to point out that in RA patients, cerebral focal stroke (ischemic or hemorrhage) can also due to systemic serum hyper-viscosity associated with the elevated titers of circulating RF.

(1.4.2) Chiari malformation

Chiari malformation is a disorder of uncertain origin that has been conventionally defined as downward herniation of the cerebellar tonsil through the foramen magnum, attributable to overcrowding of the hindbrain in a posterior cranial fossa. Among RA patients, there are few cases of acquired Chiari malformation following progression of atlantoaxial vertical subluxation. Midsagittal MR imaging, the best plane for assessing for the presence of Chiari I malformations, depicts vertical AAS, distance from the tips of the cerebellar tonsils to Chamberlain's line > 5mm (from the posterior margin of the hard palate to the posterior margin of the foramen magnum), "peg-like" aspect of the tonsils (pointed, rather than rounded) and "sergeant stripes" sulci (vertically orientated). The association between rheumatoid AA subluxation and syringomyelia is rare. Severe rheumatic craniocervical disease with vertical subluxation may reduce the rate of ascent of cerebrospinal fluid in the vertebral column by reducing the available space in the foramen magnum. Subsequently, cerebrospinal fluid would travel through the spinal cord as the path of least resistance, thus causing syringomyelia. Secondly, AA disease may compress and interfere with blood supply to the spinal cord, leading to ischaemia, necrosis and cavity formation (Fig. 7).

(1.5) Intracranial hypotension

Spontaneous intracranial hypotension (IH), caused by a reduction in CSF volume and pressure, can also be encountered in patients with rheumatoid dural or vertebral involvement resulting in a CSF leak. Orthostatic headache is the most common clinical symptom that should ring a bell. Cerebral MRI signs of IH are (Fig. 8):

- diffuse pachymeningeal thickening and enhancement,
- subdural collections,
- venous congestion,
- globular hypophysis,
- "slit" appearance of the third ventricle
- signs of downward displacement of the brain (such as kneeling of the midbrain, reduced bridge-clivus distance and tonsillar herniation)

(1.6) Proton magnetic resonance spectroscopy ($^1$H-MRS)

Recent studies have demonstrated the presence of significant neurochemical changes in the brain of RA patients with active systemic inflammation but without cerebral abnormalities on MRI. $^1$H-MRS of the periventricular normal-appearing white matter in RA patients, compared with that in healthy controls, shows a positive correlation between choline-to-creatine ratio with the erythrocyte sedimentation rate (ESR) and with overall disease activity; whereas the NAA-to-choline ratio was negatively correlated with ESR. Increased choline signals, as a marker of cell membrane turnover, could be caused by monocyte infiltration during increased disease activity, which suggests an influence of the immune system on the brain during RA. On the other hand, decreased NAA signals indicate neuronal loss. In conclusion, elevated ratios of choline-to-creatine and lowered ratios of NAA-to-choline in RA patients are associated with systemic inflammatory disease activity in the absence of abnormalities on conventional MRI sequences (Fig. 9).

(2) MANIFESTATIONS RELATED TO DRUGS

(2.1) Rituximab

PML is a demyelinating disease of the CNS that occurs almost exclusively in immunosuppressed individuals, as in RA patients in treatment with Rituximab. This disease, caused by a reactivation of the polyomavirus JC (JCV), usually manifests with subacute neurologic deficits including altered mental status, motor deficits (hemiparesis or monoparesis), limb ataxia, gait ataxia, and visual symptoms such as hemianopia and diplopia. Typically, PML is a confluent, bilateral but asymmetric, supratentorial white matter disease; however, it can be unilateral, and there may be a single lesion. In the supratentorial type, lesions are typically limited to sub- cortical U-fibers surrounded by uninvolved cortical tissue, with sparing of periventricular or deep white matter. In the infratentorial type, lesions are classically located in the middle cerebellar peduncles, frequently extending to the adjacent pons and/or cerebellum. In advanced disease, lesions can extend to the midbrain above and the medulla below. PML lesions are characteristically hypointense on T1, typically not enhancing, hyperintense to the cortex.
on T2w/FLAIR images, with a tendency to undergo coalescence and central necrotic excavation. Another typical imaging finding is absence of atrophy in the active stage. The appearance on DWI varies according to the disease stage: in new active lesions, there is a rim of diffusion restriction at the advancing edge and a central core of facilitated diffusion (the rim is usually incomplete and signifies active infection); in old "burnt out" lesions after therapy or at the center of a large lesion, there is facilitated diffusion.

(2.2) Corticosteroids

Although high levels of endogenous glucocorticoids secreted during prolonged stress may induce hippocampus atrophy, it is possible that glucocorticoid drugs may produce neuronal degeneration and reactive gliosis.

(2.3) Non-steroidal anti-inflammatory drugs (NSAIDs) - Methotrexate (MTX)

These drugs may cause serious adverse events, including neurologic syndromes, such as aseptic meningitis.
**Fig. 1:** MRI brain findings in Rheumatoid Arthritis

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Table 1: MRI brain findings in Rheumatoid Arthritis

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<th><strong>Rheumatoid vasculitis</strong>: necrotizing vasculitis of small and medium-sized vessels</th>
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Fig. 2: M, 78yo affected by diabetes, hypertension, rheumatoid vasculitis with recent (2 weeks before) left bulbar ischaemic stroke; clinical manifestations are seizures and impairment of consciousness. Brain MRI shows ischaemic lesion in the left medulla in subacute age: hyperintense on T2/FLAIR images (a,b), slight hypeintense on DWI (c) and with disruption of the blood-brain barrier (d). Coronal T2-weighted image (e) and axial FLAIR image (f) show high signal intensity of the left medial occipito-parietal cortex and the adjacent subcortical white matter; the same lesion has restricted diffusion (g) and post-contrast enhancement (h). Coronal T2-weighted image (e) also shows bilateral subdural collections. These imaging findings reflect RA-vasculitis (ischemic brain lesion and focal parenchymal lesion) and RA-related intracranial hypotension.

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Fig. 3: Rheumatoid meningitis. F. 62yo, without an history of rheumatoid arthritis; clinical onset characterized by left hemiparesis with progressive and worsening onset. Brain MRI shows abnormal signal of the subarachnoid space in the right parietal lobe, that appears hyperintense on axial FLAIR and coronal T2W images (a,b) and with bright signal on DWI (c); the diffusely increased T2/FLAIR-signal observed in the adjacent brain parenchyma (a,b), involving cortex and sub-cortical white matter, was most likely consistent with inflammatory reactive edema. Gadolinium-enhanced T1-weighted images (d,e,f) show right parietal linear leptomeningeal and pachymeningeal enhancement. Serologic results are positive for rheumatoid factors and for more specific anti-CCP antibodies.
Fig. 4: Rheumatoid meningitis. F. 75yo, with a long history of rheumatoid arthritis, affected by right hemiparesis with progressive and worsening onset. FLAIR images (a,b) show hyperintensity of the cortex and the subarachnoid space of left frontal lobe, with swelling of the cortex. SWI (c) shows point-like paramagnetic storage in the same frontal lobe as for hemosiderin deposits, in absence of vasculitic signs on both morphologic and angiographic sequences (f). DWI shows abnormal signal in the subarachnoid space (d), due to proteinaceous or fibrinoid material. Post-contrast T1WI images (e) documents extensive thick linear enhancement of the leptomeninges overlying the left frontal lobe.

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Fig. 5: Sakaguchi-Kauppi method to assess vertical atlantoaxial subluxation. Under normal situation (grade I), the tips of the facets of the axis are situated under a line drawn from the lower part of the posterior atlas arch to the lowest part of the anterior atlas arch (the lower atlas arch line). Vertical subluxation is diagnosed when the atlas falls around the axis; it is categorized into grades II, III, or IV.

**Fig. 6:** Vertical atlantoaxial subluxation (AAS) and positional occlusion of the vertebral artery. M. 46 yo, affected by rheumatoid arthritis. Sagittal T2w image of the cervical spine (c) shows vertical atlantoaxial subluxation, with the displacement of the odontoid process into the foramen magnum and impressio basilaris. Brain MRI FLAIR images (a,b) document multiple cerebellar infarctions in the territory of the vertebrobasilar artery. Insufficiency of the vertebral artery circulation must be suspected.

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Fig. 7: Chiari malformation. A 62-year-old woman with a 4-year history of RA presented with progressive neck pain. T2-weighted MRI showing progression of atlantoaxial vertical subluxation with syringomyelia at the C2-C5 levels, anterior cervico-medullary compression, and tonsillar herniation at age 65 years.

Fig. 8: Intracranial hypotension. F. 55yo, affected by rheumatoid arthritis, with a long history of orthostatic headache. Brain MRI shows most common findings of intracranial hypotension such as subdural collections (a), globular hypophysis (e), "slit" appearance of the third ventricle (b), signs of downward displacement of the brain (e) and diffuse pachymeningeal thickening and enhancement (c,d).

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Fig. 9: Proton magnetic resonance spectroscopy (1H-MRS)- Choline peak. Proton magnetic resonance spectroscopy spectra of a patient with active rheumatoid arthritis (RA), as determined by a high erythrocyte sedimentation rate (ESR) (left), a patient with inactive RA, as determined by a low ESR (middle), and a healthy control subject (right). The choline signal is markedly increased in the patient with active RA. NAA N-acetylaspartate.

Conclusion

There are several intracranial manifestations of RA, which radiologists must be aware of in order to correctly identify and interpret them.
References


