Central Nervous System Disease in Antineutrophil Cytoplasmic Antibodies–Associated Vasculitis

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KEYWORDS

- Antineutrophil cytoplasmic antibodies (ANCA) • Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangitiis (Churg-Strauss syndrome)
- Chronic hypertrophic pachymeningitis • Pituitary pseudoadenoma

KEY POINTS

- Central nervous system disease is an uncommon manifestation of granulomatosis with polyangiitis, is rare in microscopic polyangiitis, and does not occur in eosinophilic granulomatosis with polyangiitis.
- The 3 most important central nervous system manifestations of granulomatosis with polyangiitis are chronic hypertrophic pachymeningitis, pituitary disease, and cerebral vasculitis.
- Treatment of ANCA-associared CNS vasculitis often involves combination immunosuppressive regimens that include high dose corticosteroids and cytoxic agents or rituximab.

OVERVIEW

The antineutrophil cytoplasmic antibodies (ANCA)-associated diseases, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), are primary systemic vasculitic diseases. GPA is an idiopathic granulomatous necrotizing small-vessel vasculitis associated with ANCA primarily directed against proteinase 3 (PR3). Its most common clinical manifestations are granulomatous vasculitis with sinonasal inflammation and necrosis, cavitary pulmonary masses and diffuse alveolar hemorrhage, and a crescentic, pauci-immune glomerulonephritis.[1] MPA is a systemic vasculitis of small- to medium-sized vessels

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that is associated with antibodies directed against the target antigen myeloperoxidase (MPO). It usually manifests as glomerulonephritis and diffuse alveolar hemorrhage.[2] Nevertheless, both GPA and MPA are systemic disorders that can affect organ systems other than the airways and kidneys, including the central nervous system (CNS). In contrast to GPA and MPA, CNS involvement in EGPA or in PAN is very rare, if it occurs at all.

CNS involvement in GPA is widely reported and affects between 7% and 11% of GPA patients, a figure that is even higher if cranial neuropathies are also included as manifestations.[3,4] Generally, when GPA affects the CNS, it tends to involve 3 primary structures: the pituitary gland, the meninges, and the cerebral vasculature.[3,4] Although the cause of GPA remains unknown, its predilection for these areas is thought to be related to 3 distinct pathogenic mechanisms.[3] First, GPA is unique among the ANCA-associated diseases in its ability to cause granulomatous inflammation capable of invading neighboring structures. Because inflammation in GPA commonly originates in the sinonasal structures, GPA can invade the orbit, optic nerve, chiasma, cranial nerves, meninges, and pituitary gland. Second, granulomatous inflammation can occur remotely in the CNS and involve the cerebrum, meninges, cranial nerves, and parietal bone. Finally, GPA is a systemic disease, and vasculitis of small and medium arteries can occur in the CNS, including cerebral and spinal vessels, much as it can occur elsewhere in the body.[3]

PITUITARY INVOLVEMENT

Pituitary involvement is an uncommon but widely recognized complication of GPA, affecting 1.3% of GPA patients in one large longitudinal cohort.[5] Another retrospective series of 819 patients with GPA diagnosed between 1963 and 2014 reported pituitary involvement in 1.1%.[6] The median age of diagnosis of pituitary disease in these 2 studies was 48 and 50, respectively, with men and women being evenly affected in both cohorts.[5,6] Three different pathogenic mechanisms of pituitary disease have been suggested, including in situ development of granulomatous inflammation in the gland itself and vasculitis of the pituitary vessels.[5] However, the most widely accepted mechanism implicates granulomatous invasion of the pituitary from neighboring sinus cavities, a notion suggested by the observation that 16 of 17 patients in the 2 largest series of GPA-associated pituitary disease also had concomitant upper airway involvement.[5,6] Other disease manifestations of GPA were also common, with approximately one-third of patients with pituitary disease having glomerulonephritis, and others having dermatitis, arthritis, and central or peripheral nervous system involvement.[5–7]

GPA-associated hypophysitis can lead to partial or global pituitary dysfunction.[8] Both the anterior and the posterior pituitary can be affected and lead in some cases to panhypopituitarism.[5] Patients initially complain of nonspecific symptoms, including headache, generalized weakness, and fatigue, which can delay recognition of this condition. With more pronounced pituitary involvement, clinical symptoms often will reflect specific endocrinopathies. Diabetes insipidus, a sign of posterior pituitary involvement, is the most commonly reported manifestation of GPA-related pituitary dysfunction, with patients complaining of polyuria and polydipsia with elevated serum but depressed urine osmolality.[5,6,9] Secondary hypogonadism, reflecting involvement of the anterior pituitary, is also prominent and can cause menstrual dysregulation, decreased libido, loss of muscle mass, erectile dysfunction, and diminished testicular size.[5,6] Secondary hypothyroidism from diminished Thyroid Stimulating hormone production, adrenal insufficiency from reduced production of adrenal corticotropic