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Opinion

Immune Ataxias: The Continuum of Latent Ataxia, Primary Ataxia and Clinical Ataxia

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Abstract

The clinical category of immune-mediated cerebellar ataxias (IMCAs) is now recognized after 3 decades of clinical and experimental research. The cerebellum gathers about 60% of neurons in the brain, is enriched in numerous plasticity mechanisms, and presents a large variety of antigens at the neuroglial level: ion channels and related proteins, synaptic adhesion/organizing proteins, transmitter receptors, and glial cells. Cerebellar circuitry is especially vulnerable to immune attacks. After the loss of immune tolerance, IMCAs present in an acute or subacute manner with various combinations of a vestibulocerebellar syndrome (VCS), a cerebellar motor syndrome (CMS), and a cerebellar cognitive affective syndrome/Schmahmann's syndrome (CCAS/SS). IMCAs include gluten ataxia (GA), post-infectious cerebellitis (PIC), Miller Fisher syndrome (MFS), paraneoplastic cerebellar degeneration (PCD), opsoclonus myoclonus syndrome (OMS), anti-glutamic acid decarboxylase (anti-GAD) ataxia, and glial fibrillary acidic protein (GFAP) astrocytopathy (GFAP-A). In addition, multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), Behçet disease, and collagen-vascular disorders may also present with cerebellar symptoms when lesions involve cerebellar afferences/efferences. Patients whose clinical profiles do not fit with IMCAs are now gathered in the group of primary autoimmune cerebellar ataxias (PACAs). Latent auto-immune cerebellar ataxia (LACA) refers to a clinical stage with a slow progressive course and a lack of obvious auto-immune background. At a pre-symptomatic stage, patients remain asymptomatic, whereas at the prodromal stage aspecific symptoms occur, announcing the symptomatic neuronal loss. LACA corresponds to a time-window where an intervention could lead to preservation of plasticity mechanisms. Patients may evolve from LACA to PACA and typical IMCAs, highlighting a continuum. Immune ataxias represent a model to elucidate the sequence of events leading to destruction of cerebellar neuronal reserve and develop novel strategies aiming to restore plasticity mechanisms.

Keywords: cerebellum; ataxia; immune; tolerance; reserve; therapies

1. Introduction

The cerebellar circuitry contains about 60% of the neurons in the brain and is a site for plasticity mechanisms underlying motor learning, cognition, and behavior [1–3]. The cerebellum is characterized by a high diversity of cells and antigens located in the extra-cellular/intracellular structures [4,5]. Cerebellar circuitry has a unique geometric arrangement of densely packed neurons and glial cells enriched in proteins for ion channels or receptors, particularly suited to monitor brain functions and implement corrective signals via numerous cerebello-cerebral loops running in parallel.

The cerebellum is particularly vulnerable to immune diseases. During the last 3 decades, a group of immune-mediated cerebellar ataxias (IMCAs) have been identified as a category of neuroimmune disorders. IMCAs include gluten ataxia (GA: associated with gluten sensitivity and developing in some cases without intestinal symptoms; the autoantigen is tissue transglutaminase), post-infectious cerebellitis (PIC: context of infection), Miller Fisher syndrome (MFS: a form of Guillain-Barré syndrome associated in particular with antibodies anti-GQ1b), paraneoplastic cerebellar degeneration (PCD: the immune response is directed against neuronal antigens expressed by tumor cells and neurons), opsoclonus myoclonus syndrome (OMS: an immune disease usually triggered by cancer or infection), anti-glutamic acid decarboxylase (anti-GAD) ataxia (antibodies impact GABAergic (GABA, gamma-amino-butyric) transmission and the shuttling of GABAergic synaptic vesicles to the synaptic cleft), and glial fibrillary acidic protein (GFAP) astrocytopathy (GFAP-A: a steroid-responsive meningoencephalitis manifesting with movement disorders including cerebellar ataxia) [6–12]. Other forms of secondary ataxias include steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), ataxia associated with rheumatological diseases such as systemic lupus erythematosus (SLE), and demyelinating diseases such as multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) [4,6,9,10]. It has been established that antibodies may specifically target cerebellar microcomplexes (the structural and functional units of the cerebellum) and alter synaptic mechanisms; hence the ter-

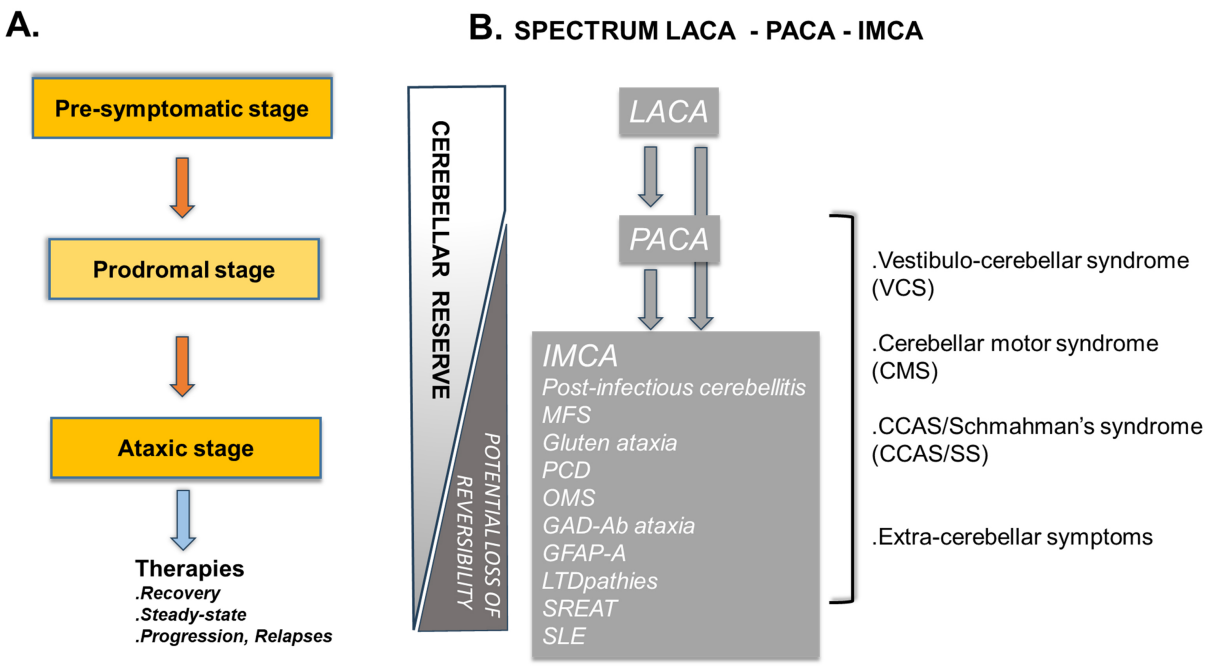

Fig. 1. Evolution of the disorders. (A) Current appraisal of the progression of cerebellar disorders from a pre-symptomatic stage to a prodromal stage announcing the disease. Patients evolve subsequently to an ataxic stage with a combination of clinical signs. At this stage, therapies may improve partially/fully the clinical status (recovery), stabilize the situation to a steady-state, or be followed by progression and relapses requiring adaptation of therapies. (B) Continuum from latent auto-immune ataxia (LACA; latent stage) to primary autoimmune cerebellar ataxia (PACA; primary auto-immune) and full stage of well identified immune ataxia (IMCA). The cerebellar reserve starts to be impacted at an early stage (possibly at the LACA stage) but is recoverable if therapies are administered early. Immune-mediated cerebellar ataxias (IMCAs) include post-infectious cerebellitis, Miller-Fisher syndrome (MFS), gluten ataxia, paraneoplastic cerebellar degeneration (PCD), opsoclonus-myoclonus syndrome (OMS), anti-glutamic acid decarboxylase (anti-GAD) ataxia (ataxia associated with GAD-antibodies), glial fibrillary acid protein astrocytopathy (GFAP-A), long-term depression related disorders (LTDpathies), steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), systemic lupus erythematosus (SLE). Multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), Behçet disease, and other collagen-vascular disorders typically involving cerebellar afferences/efferences and are not shown. After a period, when the IMCA has progressed, both the recoverability and cerebellar reserve may be reduced. In other words, the reversibility may be impacted by time loss.

minology of synaptopathies [13,14]. The group of IMCAs present typically with a subacute or acute disease course evolving from days to weeks, leading to several blends of a vestibulocerebellar syndrome (VCS; the main initial complaint is dizziness/vertigo and the lesion is located at the level of cerebellar lobules V–VII/IX–X), a cerebellar motor syndrome (CMS; the main initial complaint is clumsiness/irregular gait and the lesion is located at the level of lobules I–VI/VIII), and a cerebellar cognitive affective syndrome/Schmahmann's syndrome (CCAS/SS; the main observation is an aberrant behavior and the lesion is located at the level of lobules VI–IX in the posterior lobe). The core deficit is dysmetria (motor, cognitive, and even social function) and is currently explained by the impact of an immune attack on internal models generated and updated by the cerebellum [15–18]. Indeed, cerebellar circuitry is currently understood as a learning machine supplemented with plasticity mechanisms both at the cerebellar cortical and nuclear level allowing for adaptation to the external world.

2. Primary Autoimmune Cerebellar Ataxia (PACA)

Initially, clinicians struggled to identify IMCAs as they can be challenging to diagnose at early stages [19–21]. When an auto-immune disease is suspected, in absence of specific antibodies or other biomarker, the diagnosis of primary autoimmune cerebellar ataxia (PACA) is raised in the following conditions [20]:

-patient exhibits an acute or subacute cerebellar syndrome in absence of known genetic disorder causing ataxia such as an autosomal dominant spinocerebellar ataxia (SCA),

-cerebrospinal fluid (CSF) analysis shows a pleocytosis and/or positive oligoclonal bands,

-history of other autoimmune disorders or family history of autoimmune disorders in first degree relatives,

-presence of antibodies that support autoimmunity but not yet shown to be directly involved in ataxia pathogenesis or be markers of ataxia with a known trigger.

PACA corresponds to an umbrella that covers heterogeneous etiologies [20,21]. Most patients with PACA develop a slow progressive ataxia between 40 and 60 years of age, often with gait difficulties or lack of balance as the primary symptom. In some patients, the onset is acute and the differential diagnosis is mainly a PIC or a PCD. Brain magnetic resonance imaging (MRI) may show slight cerebellar atrophy predominating in the vermis. Other additional autoimmune diseases commonly observed include thyroiditis, diabetes, pernicious anemia, lupus, dermatitis herpetiformis, or vitiligo [4,20]. Some patients with PACA may evolve subsequently into one of the IMCAs, probably because of the deleterious effects of the neuroimmune cascade. As the immune attack progresses (activation of lymphocytes and monocytes, cellular invasion through the blood-brain barrier, release of cytokines and antibodies) more antigens from neural/glial cells become accessible to attack, and the neuroinflammation process continues [4].

3. Latent Autoimmune Cerebellar Ataxia (LACA)

The concept of latent auto-immune ataxia (LACA) has been developed by analogy with the latent auto-immune diabetes (LADA) in adults where anti-GAD antibodies are the sole biomarker and patients commonly show auto-immune diseases of thyroid gland or stomach [22–24]. In LADA, glucose regulation becomes markedly impacted over a period of 5 years, leading to diabetes due to destruction of pancreatic beta-cells. Patients who did not require insulinotherapy at the first stage become dependent on insulin due to loss of beta-cells' reserve capacities [23]. Notably, LADA shows a lack of autoimmunity at the early stage.

LACA is thus characterized by a slow progressive course and a lack of noticeable auto-immune disorder. The auto-immune etiology is present but not easily detectable because it is subclinical. The concept of LACA has to be viewed in the current approaches aiming to identify the presymptomatic stage (patients are free of ataxia) and the prodromal stage (unspecific symptoms often overlooked such as fatigue appear) (Fig. 1). LACA corresponds to the time-window where neuronal plasticity at the cerebellar cortex or cerebellar nuclei levels may still be preserved. As an example of prodromal signs, brainstem attacks may precede the manifestation of cerebellar ataxia in some patients with IMCAs [25–27]. For instance, prodromal transient neurological symptoms composed of episodes of vertigo and fluctuating diplopia may proceed ataxia onset by several weeks. In addition, organ-specific autoimmune disorders are also identified as prodromal signs [25,28].

In daily practice, the diagnosis of LACA represents a major challenge. Development of sensitive/specific biomarkers is a key step to render this concept easily applicable in clinical settings at a stage where patients are asymptomatic or poorly symptomatic despite the cerebellar reserve (which can be understood as the property of the cerebellar circuit to re-implement function in response to an attack) being weaken [29,30]:

-in fluids: blood, CSF, urine, others (e.g., saliva, tears),

-neurophysiological (e.g., transcranial magnetic stimulation (TMS)/repetitive transcranial magnetic stimulation (rTMS), posturography, gait analysis),

-morphological/functional (e.g., MRI, functional magnetic resonance imaging (fMRI), magnetic resonance (MR) spectroscopy, transparent exopolymer particles (TEP)),

-neuropsychological,

-multimodal approaches combining several tools and tailored to each case.

4. Neuroinflammation and Immune Tolerance

Neuroinflammation and immunity impact elemental neurophysiological properties such as excitability, inhibitory, and excitatory mechanisms of the microcircuitry of the cerebellum [31–34]. Inflammation impairs neurotransmission of the mossy fibers coming from numerous extra-cerebellar sources, the climbing fibers originating from the inferior olive, the cerebellar cortex, and cerebellar nuclei. Long-term depression (LTD) at parallel fibers-Purkinje cells (PF-PC LTD), a key-mechanism of cerebellar motor learning [35–37], is also impaired in IMCAs [24]. LTD results in a reduction in glutamate release.

The brain is separated from the periphery by the blood–brain barrier (BBB), the blood–CSF barrier (at the level of choroid plexus), and the blood–leptomeningeal barrier (BLMB) [38–41]. The entry of immune cells to the central nervous system for immune surveillance occurs at the blood-CSF barrier. Both microglia and peripheral immune cells contribute to immune surveillance. Microglia act as resident immune cells, through involvement in the innate immune system. The BBB and BLMB block the entry of immune cells in physiological conditions, whereas the blood-CSF barrier allows the migration of lymphocytes [42]. Chemokine receptors and interactions between integrins and cell adhesion molecules allow lymphocytic entry in the CSF. Most of the white blood cells in the CSF are T cells, B cells, dendritic cells, and monocytes-macrophages [42].

In case of auto-immune attack, an invasion of peripheral immune cells evolves in the central nervous system (CNS). The underlying mechanisms leading to the disruption of immune tolerance and subsequent infiltration of effecter T cells into the CNS remain elusive. The breakdown in the barrier permeability allows the entry of peripheral immune cells in the cerebellar compartment at the BBB, the blood–CSF barrier, or the BLMB, possibly by a mechanism of molecular mimicry between the trigger event and a host protein. In case of PCD, the autoimmune response is possibly triggered when proteins circumscribed to immune

privileged neurons are reachable by the cancer, launching a cytotoxic T-cell response, and/or a direct pathogenic effect of antibodies when surface receptors are the target antigens. An additional factor contributing to the disruption of immune tolerance is the impairment of anergy, a process that inhibits T cell activation [43]. This impairment occurs when T cells, despite recognizing an antigen, fail to receive the necessary co-stimulation. Moreover, it has also been noted that regulatory T cells (Tregs), which are integral to the suppression of immune response, exhibit dysfunction in the context of autoimmune neuronal diseases [43].

5. Therapies of Immune Ataxias

PACA and IMCAs are potentially treatable (e.g., with steroids, immunoglobulins, plasmapheresis, maintenance immunotherapy, eradication of the trigger) and should therefore be recognized promptly, as the early treatment is associated with a better outcome. Ataxiologists should carefully examine the possibility of slow evolving IMCA and take advantage of the physiological properties of the cerebellum. Indeed, the cerebellum has an inherent resilience to re-implement vanished functions thanks to profuse synaptic plastic mechanisms and conjunction of multimodal signals [44–48].

Research to identify LACA should be promoted in order to promote *prevention* of immune ataxias, a field which is currently neglected. Predictive biomarkers should be searched for and implemented in daily practice, applying a personalized approach including genetic predisposition, prognosis factors, and a close follow-up with longitudinal observations. For instance, younger onset age, presence of peripheral neuropathy/radiculopathy, and increased CSF protein concentration are relapsing factors of PACA, while absence of peripheral neuropathy/radiculopathy and response to first-line immunotherapy are associated with a favorable outcome [49].

6. Future Prospects

As for LADA, both adaptive immunity and innate immunity might be instrumental in the mechanisms of LACA [24]. Because the intestinal microbiota impacts host immunity [50,51], it's contribution in the pathogenesis of LACA/PACA/IMCA requires detailed studies. This should be explored in terms of prevention in the near future as the gut-brain axis is now discussed as a source of neurodegeneration, and there is a link between the gut microbiome and BBB integrity [52,53]. We anticipate that if a gut dysbiosis is demonstrated, this might lead to early gut microbiome-targeted approaches (e.g., probiotics, prebiotics, synbiotics, postbiotics, fecal transplantation) to prevent progression from LACA to PACA or IMCA, with potentially irreversible damage and clinical sequelae. GA is an example of immune disease where studies are ongoing to clarify the effects of diet upon the gut-brain axis. It is interesting to note that early adherence to a gluten-free diet leads to a more rapid improvement of symptoms. The expression of peroxisome proliferator-activated receptor (PPAR)-gamma gene is markedly reduced in GA and down-regulation of PPAR-gamma changes the composition of the microbiota [54]. A "leaky gut" might favor neuroinflammation. Some gut bacteria themselves contribute to the metabolism of gluten. These events should be studied in other IMCAs. Another observation is the common co-occurrence of gastrointestinal symptoms in autism-spectrum disorder (ASD). Cerebellar pathology is well known in ASD, an immune dysfunction is suspected, both in animal models of ASD and in human, and dysbiosis is now suspected in these patients.

Inflammation triggers a marked increase of immune cells in the CNS [42,55]. The BBB becomes more permeable to solutes, shows an increase in lymphocyte trafficking, and becomes a site of infiltration by innate cells [55]. In the majority of auto-immune conditions affecting the cerebellum, both the BBB and the blood-CSF barrier become compromised [42]. Once the breakdown has started, it tends to spread locally. The BBB of the cerebellar circuitry appears to be more permeable compared to other brain regions. It is therefore conceivable that therapies aiming to block the transmigration of immune cells at a very early step when the patients are a LACA stage might stop the immune attack and prevent the cerebellar injury. This can be envisioned provided that reliable biomarkers of LACA have been identified. In a recent study gathering 127 cases of IMCAs, 13 patients died and 24 patients relapsed [21], stressing the need for an early detection before progressing to a full set of cerebellar symptoms.

7. Conclusions

In conclusion, LACA can be considered as a time-window where therapies could lead to conservation of plasticity and cerebellar functions. Patients may progress from LACA to PACA, and subsequently to typical IMCAs. A continuum in the natural course of immune ataxias has emerged, with a great challenge in terms of diagnosis for LACA and PACA. Immune ataxias represent a unique model to clarify the sequence of events causing the destruction of cerebellar neuronal reserve and propose novel therapeutical approaches towards a full reinstatement of cerebellar plasticity mechanisms.

Abbreviations

ADEM, acute disseminated encephalomyelitis; CCAS/SS, cerebellar cognitive affective syndrome/Schmahmann's syndrome; CMS, cerebellar motor syndrome; GA, gluten ataxia; GFAP-A, glial fibrillary acidic protein astrocytopathy; IMCA, immune-mediated cerebellar ataxia; LACA, latent auto-immune cerebellar ataxia; MFS, Miller Fisher syndrome; MS, multiple sclerosis; OMS, opsoclonus myoclonus syndrome; PIC, post-infectious cerebellitis; PACAs, primary autoimmune cerebellar ataxias; PCD, paraneoplastic cere-

bellar degeneration; SLE, systemic lupus erythematosus; SREAT, steroid-responsive encephalopathy associated with autoimmune thyroiditis; VCS, vestibulocerebellar syndrome.

Author Contributions

Literature search, conception, drafting, approval of final version: MM, HM. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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