Review article

INBORN ERRORS OF IMMUNITY IN PAEDIATRIC NEUROLOGY

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ABSTRACT
Inborn errors of immunity has become a rapidly evolving medical field, with nearly 500 conditions; as a result, the sheer volume of information can be overwhelming. In order to make a sound diagnosis, clinicians must adopt an integrative approach and identify all related and seemingly unrelated features. It is therefore crucial to understand the complex networks and interactions between organelles, cells, pathways and organ systems thoroughly. The immune system is an important stakeholder in all these networks. It is designed to be our friend, defending and protecting us by regulating tolerance. However, it can also turn into an enemy. Every individual has their own unique combination of genetic predisposition, trigger factors and environmental factors that contribute to the spectrum of neurological diseases. The main objective of this article is to create a mind map that starts with the clinical presentation.

Keywords: inborn errors of immunity, neurology, genetic predisposition, paediatric, networks

INTRODUCTION

Inborn errors of immunity (IEI), previously called 'primary immunodeficiencies' (PIDs), is a rapidly evolving medical field with almost 500 conditions.[1] The amount of information is overwhelming for the majority of clinicians. However, it remains crucial to identify all the related and seemingly unrelated features to make a sound diagnosis. Practising medicine in this era requires an integrative approach to managing patients more than ever before. An integrative approach requires a thorough understanding of the complex networks and interactions between organelles, cells, pathways and organ systems. Following a systems biology approach broadens our understanding of the complex networks of interactions, signalling and regulating mechanisms in the human body.[2]

In systems biology, models are built using mathematical and computational analyses of the massive 'omics' datasets, including genomics, transcriptomics, proteomics, metabolomics, regulonomics and signalomics in cells, organs and organisms. Ultimately, it helps us to interpret complex symptom combinations, explain previously undiagnosed phenotypes and identify possible biomarkers that might improve a diagnosis.[2]

An important stakeholder in all these networks is the immune system. It is designed to be our friend, defending and protecting us through tolerance regulation. However, it can also turn into an enemy.

This article is not intended to be a comprehensive review. Our goal is to create a mind map for clinicians to help them to understand the neurological manifestations within primary immunity (see Figure 1).[1,3–7]

HOW AND WHY IS THE NEUROLOGICAL SYSTEM AFFECTED?

The mind map in Figure 1 is designed to help the clinician by starting with clinical features and then explaining all the factors that determine the spectrum of neurological disease. Neurological manifestations in the central nervous system (CNS) or the peripheral nervous system (PNS) without a definitive explanation should always alert the clinician to at least considering the possibility of an IEI in the differential diagnosis. This should apply especially if it is combined with red flags signs of IEI, including frequent severe or unusual infections, allergies, autoimmune disorders and less common malignancies. These symptoms may present either at the onset or later during the disease.[4]

The symptoms may be subtle, may vary and may initially be regarded as insignificant. They compel careful follow-up of patients and thorough assessment with every follow-up visit. The symptoms associated with the CNS may include, but are not limited to, these:[4]

- cognitive impairment and learning disabilities
- developmental delay (eg DiGeorge syndrome also known as 22q11.2 deletion syndrome)
- impaired memory and concentration
- psychiatric manifestation
  - confusion
  - irritability
  - hallucinations
  - depression
- abnormal reflexes
- ataxia (eg ataxia-telangiectasia)
- nystagmus
- impaired balance

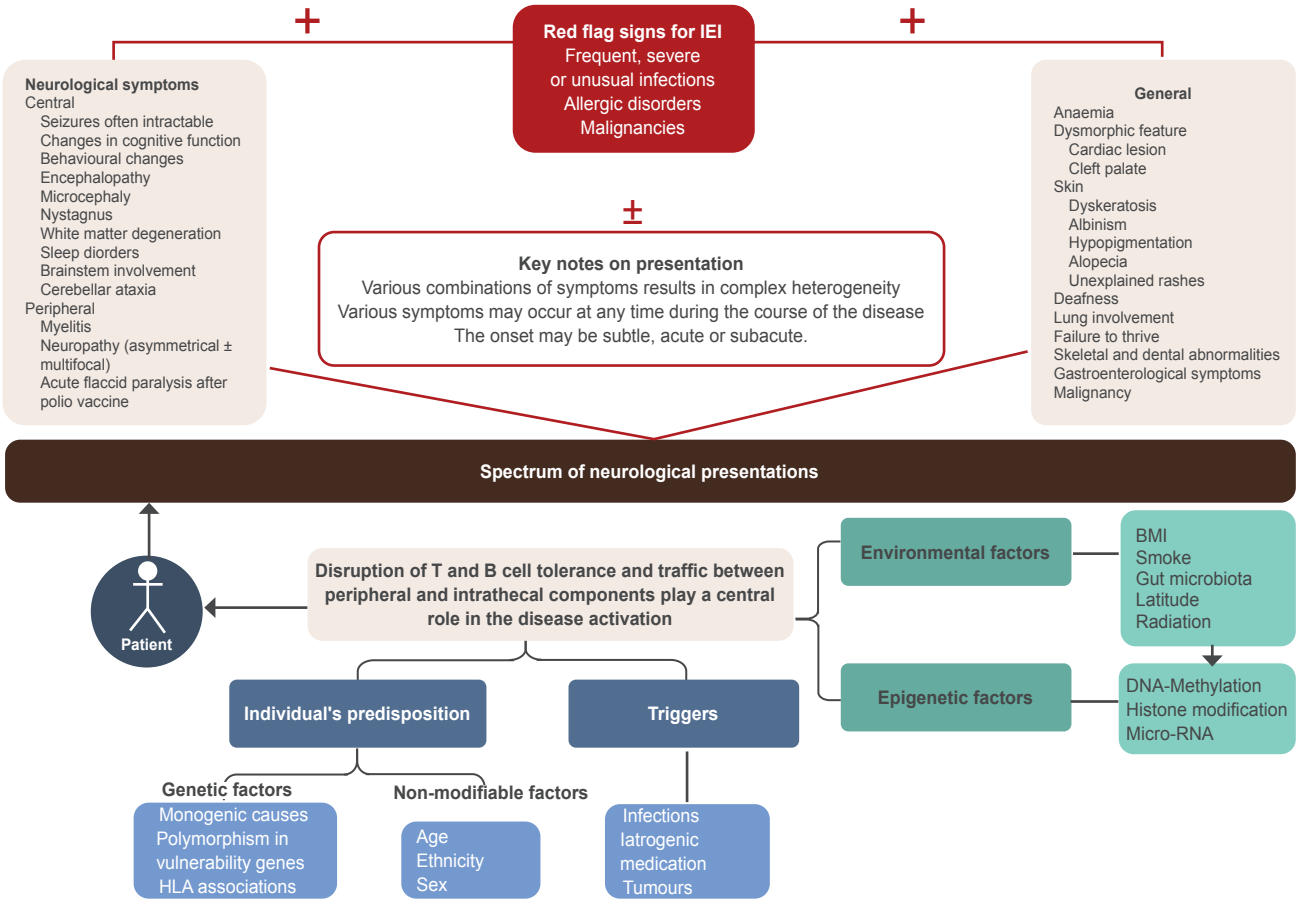

Figure 1: The how and why of inborn errors of immunity present with neurological manifestations and red flags when to suspect them[1,3–7] (BMI, body mass index; HLA, human leucocyte antigens; IEI, inborn errors of immunity; RNA, ribonucleic acid).

- microcephaly
- acute flaccid paralysis after polio vaccination (associated with combined immunodeficiency (CID))
- spinal and peripheral neuropathies
- seizures
- sensorineural deafness
- movement disorders
- early onset stroke
- hypotonia
- spasticity.

General symptoms include: [8]

- dysmorphic features
  - o abnormal craniofacial dysmorphisms
  - o cleft palates
  - o cardiac defects
  - o neural tube defects
- failure to thrive
- pernicious anaemia may present later with common variable immune deficiency (CVID)
- skin manifestations
  - o telangiectasia
  - o dyskeratosis
  - o albinism
  - o hypopigmentation.

In considering an IEI in the differential diagnosis for a patient, a prerequisite is that the clinician understands the pathophysiology. The terminology of IEI reflects the genetic nature of PIDs that makes a clear distinction from secondary immune deficiency caused by malnutrition, infections (eg human immunodeficiency virus (HIV)), radiotherapy and chemotherapy. Furthermore, an individual's genetic predisposition is determined by their unique genotype and the influence of non-modifiable factors (sex, age and ethnicity). Various possible trigger factors should accordingly be considered in an individual's risk of developing immune-related conditions affecting the CNS.

These factors include:

- the major histocompatibility complex (MHC), also known as the human leucocytes antigen (HLA) locus;[9]
- single nucleotide polymorphisms (SNPs) associated with an increased risk of developing autoimmune disease, which are clustered in genes involved in the immunological pathways;[3]
- infections in which the microbial antigen impersonates the self-antigen, leading to antibodies against an organism to react with the self-antigen;[3]
- natural auto-antibodies that may be activated by tissue damage or an infection, turning into high-affinity antibodies and subsequent autoimmune disease;[10]
- gut microbiota that may activate autoreactive T-cells in the gut-associated lymphoid tissue and enable them to cross the blood–brain barrier (BBB);[11]
- epitope spreading in which there is a diverse immune

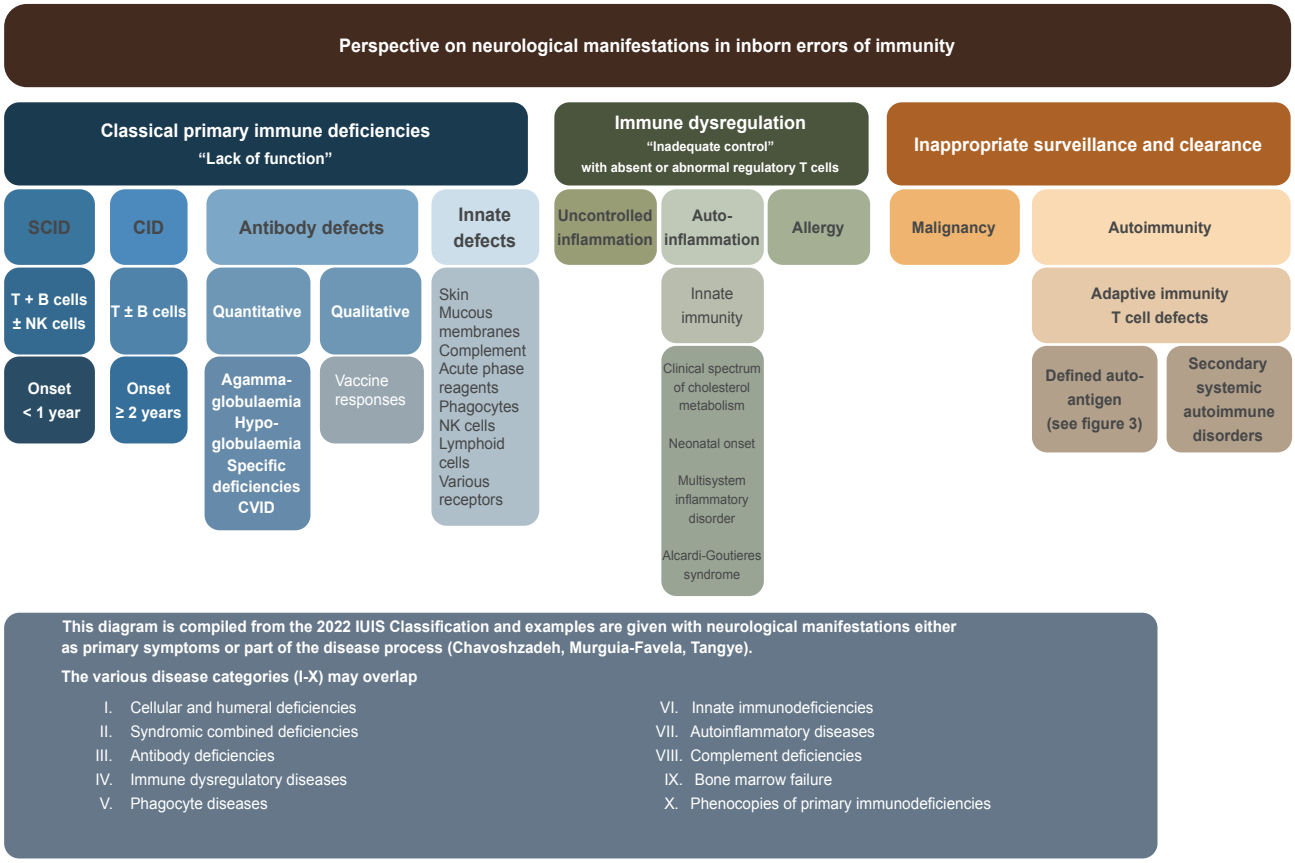

Figure 2: Neurological manifestations in the spectrum of inborn errors of immunity[1,3,6] (CID, combined immune deficiency; IUIS, International Union of Immunological Societies; LRTI, lower respiratory tract infection; NK cells, natural killer cells; SCID, severe combined immune deficiency; URTI, upper respiratory tract infection)

response to the part of the antigen recognised by the immune system;[12]
- onconeural antigens in paraneoplastic syndromes;[13]
- vitamin D and its effect on the regulation of the immune system.[14]

Their ever-changing environment complements an individual's unique genetic predisposition. Environmental factors such as smoke, radiation, latitude, gut microbiota and an abnormal body mass index (BMI) can alter the DNA and histones chemically through DNA methylation and histone modification. This can affect gene expression and result in alternative phenotypes without changing the nucleotide sequence. These changes are stable and can be passed down through inheritance.[15]

PERSPECTIVE ON NEUROLOGICAL MANIFESTATIONS

Recent studies have shown that the CNS is not immune-privileged and that there can be communication between the peripheral and the intrathecal components. If the tolerance of T- and B-cells is disrupted due to various factors, this can trigger diseases and result in a range of neurological conditions.[7]

When a patient presents with neurological symptoms and an IEI is suspected, the updated classification of the International Union Immunological Society (IUIS) can be overwhelming, with its ten disease categories.[1] However, for practical purposes, it may be helpful for clinicians to consider three major disease groups broadly, as illustrated in Figure 2.

The three groups of disorders reflect the underlying immune system mechanisms.[6] The first group comprises disorders that result in a lack of immune function and an increased risk of infections. These are known as classical primary immune deficiencies, including cellular and humeral ones. The cellular defects may involve T, B and natural killer (NK) cells and they typically manifest as severe combined immunodeficiency disorders (SCID), usually occurring in the first year of life. In contrast, NK cells are not involved in CID and may present from two years of age until adulthood. Well-known conditions in this group include DiGeorge syndrome (22q11.2 deletion syndrome), ataxia telangiectasia (A-T) and hyper-IGM syndromes. Recurrent infections are expected if the antibodies are affected quantitatively or qualitatively and the type of infection may indicate the underlying defect.

The last sub-group includes conditions affecting innate immunity, of which Chediak-Higashi syndrome is a typical example.[4,6]

The second group is a result of immune dysregulation.[6] It comprises absent or abnormal regulatory T-cells (Tregs). The outcome is inadequate control and uncontrolled inflammation, auto-inflammation and allergies. The auto-inflammation is

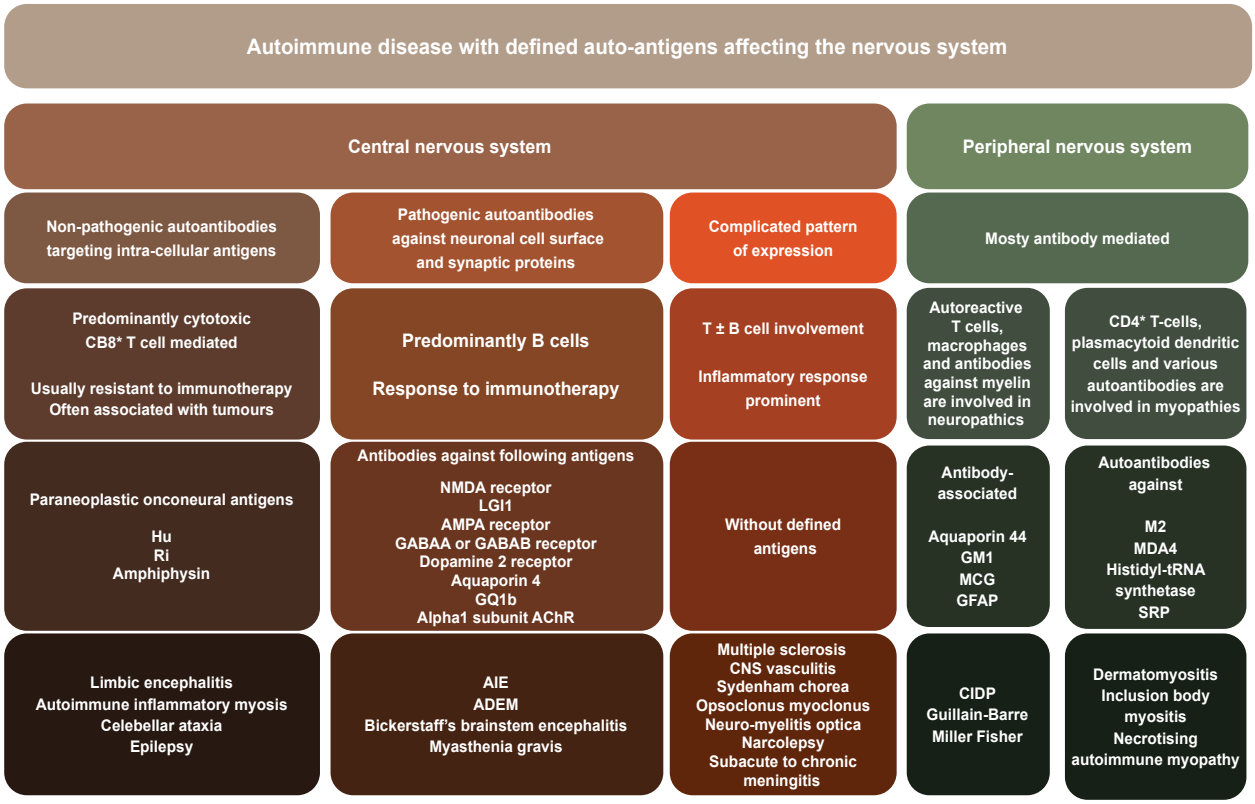

Figure 3: Autoimmune disease affecting the central and peripheral nervous system

Compiled from[3–7]. (AChR, acetylcholine receptor; ADEM, acute demyelinating encephalomyopathy; AIE, autoimmune encephalomyelitis; AIM, autoimmune inflammatory myositis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNS, CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; GABA, Gamma-aminobutyric acid; GAD, glutamic acid decarboxylase, GFAP, Glial fibrillary acidic protein; GM1 and GQ1b, types of ganglioside antibody; MDA, malondialdehyde; Mi2, Mi-2 antigen is a component of the nucleosome remodelling-deacetylase; MOG, Myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMDA, N-methyl-d-aspartate; NMO, neuromyelitis optica; SRP, signal recognition particle).

associated with the innate immune system, with multisystem involvement. Aicardi-Goutières syndrome (AGS) is a well-known condition affecting the neurodevelopment, skin and immune system. It is the result of the accumulation of endogenous RNA that triggers interferon-α production, activating neurotoxic lymphocytes and inhibiting angiogenesis. These patients may present with infantile spasms, spasticity, microcephaly and dystonia.[4]

The third group results from inappropriate surveillance and clearance, resulting in various malignancies and autoimmunity.[6] With the autoimmunity-related disorders, T-cells and adaptive immunity are affected. These outcomes can be secondary to systemic autoimmune disorders or a defined auto-antigen can be identified. They can present at any age or any stage in the course of an IEI.[6] The approach to autoimmune disease with defined auto-antigens affecting the CNS is presented in Figure 3.

AUTOIMMUNITY AND THE NERVOUS SYSTEM

Currently, around 30 neurological conditions are attributed to an autoimmune-related mechanism and in the review by Bhagavati (2021), the clinical features, pathophysiology and therapies are discussed eloquently.[3] Clinical features that may be indicative of a possible autoimmune disease are:

- acute or sub-acute onset of deterioration in cognitive function, behavioural changes and intractable seizures, provided infection is excluded;
- faciobrachial dystonic seizures;
- recent onset of psychiatric symptoms, for example, aggression, hallucinations, delusions, disinhibition, mutism and catatonia in a previously healthy patient;
- subacute onset of cerebellar ataxia with or without brainstem involvement, myelitis or neuropathy;
- sleep disorders;
- movement disorders;
- neuromyotonia;
- autonomic disturbances;
- asymmetric, multifocal sensory neuropathies with loss of proprioception and subacute sensory ataxia.[3]

The presentation of autoimmune diseases affecting the nervous system depends on the location of antigenic targets, which can be either intracellular or on the surface of neurons. However, more complex mechanisms are also described in an extensive review of the various antigens and antibodies.[3] The CNS autoimmune-related disease can be divided into three groups, although there may be an overlap between the broad groups.

The first group includes disorders associated with non-pathogenic autoantibodies (eg anti-GAD65, anti-Hu and anti-

Ri) against intracellular antigens. These disorders are often associated with an underlying malignancy (eg malignant thymoma, neuroblastoma and breast cancer). Typical clinical manifestations include limbic encephalitis, cerebellar ataxia and epilepsy. This group of neurological disorders is frequently resistant to immunotherapy and predominantly mediated by cytotoxic CD8+ T-cells. For more detailed information, refer to the comprehensive lists.[3,7]

The second group includes conditions associated with pathogenic autoantibodies against neuronal cell surface or synaptic proteins. These conditions involving predominantly B-cells are known to be responsive to immunotherapy and include autoimmune encephalitis associated with antibodies against antigens such as NMDA receptor, GABAA/B, glycine receptor. Antibody-associated demyelination is associated with Aquaporin 4, glial fibrillary acidic protein (GFAP) and myelin oligodendrocyte glycoprotein (MOG). Clinicians may be familiar with conditions in this group, such as Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), optic neuritis and many others.[3,5,7]

A third sub-group of autoimmune diseases affecting the CNS involves a complex immune response with T- and sometimes B-cells but no defined antibodies.[3] This group of disorders is illustrative of the interaction between cells, the environment and genetic predisposition. Multiple sclerosis (MS) is a perfect example. It is strongly associated with HLA and active lesions containing abundant B-cells. CD20+ B-cells, CD138+ plasma cells and follicular dendritic cells were found in the leptomeninges of MS patients. Plasma cells and plasmablasts targeting neurons, astrocytes and oligodendrocytes have also been observed. Antibodies against rubella, measles and varicella-zoster can be detected in the cerebrospinal fluid; however, the target antigen is unknown.[3] It is postulated that the humoral B-cell response may be directed against various self- and non-self-antigens due to epitope spreading, resulting in secondary immune-related damage to the CNS. Individuals exhibit varying responses.[3]

Autoimmune manifestations in the peripheral nervous system (PNS) are mostly antibody-driven. Autoreactive T-cells, macrophages and antibodies against myelin are involved in neuropathies. Well-known conditions are GBS, chronic inflammatory demyelinating polyneuropathy and Miller Fischer syndrome (MFS); they are hallmarked by antibody-associated demyelination against Aquaporin 4, glial fibrillary acidic protein (GFAP), GM1 and GQ1b types of ganglioside antibodies and myelin oligodendrocyte glycoprotein (MOG).[3]

When the muscle is affected, CD4+ T-cells, plasmacytoid dendritic cells and various antibodies can all be found. Examples of these antibodies are those against Mi-2 antigen, which is a component of the nucleosome remodelling-deacetylase, histidyl tRNA synthetase or signal recognition particles (SRP). Dermatomyositis, inclusion body myositis and necrotising autoimmune myopathy (NAM) are examples of conditions that fall into this group. Generally, these conditions respond well to immunotherapy.[3]

In this article, we have only scratched the surface of autoimmune-related conditions affecting the CNS and the PNS. However, the field is rapidly evolving in the areas of aetiology and pathogenesis and potential treatment modalities.

CONCLUSION

Adopting a systems biology approach can help to uncover the underlying mechanisms of IEI while emphasising the importance of an integrated approach in clinical medicine. Doing so requires clinicians to recognise the symptoms in systems unrelated to their primary field of interest and to avoid delaying an accurate diagnosis in order to manage the condition optimally and prevent avoidable complications.

CONFLICT OF INTEREST:
The authors declare no conflict of interest.

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