Chapter

Perspective Chapter: Red Flags for Syndromic Epilepsy

Bita Shalbafan

Abstract

Despite the high frequency of seizures and propensity to develop status epilepticus (SE) most cases do not develop a long-term predisposition to seizures. So, investigating a patient with refractory epilepsy or unexplained status epilepticus is important to consider the possibility of treatable diseases i.e. treatable types of inborn error of metabolism, paraneoplasia, infections, and TLE due to temporal lobe encephalocele and IIH. Epilepsy syndrome (ES) refers to a cluster of features that should be paying attention to its red flags to narrow the wide differential diagnosis.

Keywords: syndromic epilepsy, paraneoplasia, inborn error of metabolism, encephaloceles, new-onset refractory status epilepticus

1. Introduction

Epilepsy can be observed during the course of many usually as part of a large clinical spectrum. Epilepsy Syndrome diagnosis step-by-step approach starts in the first level to detect seizure type semiologically, then Epilepsy type detection as the second level, *epilepsy syndrome* (ES) is diagnosed based on any co-morbidity in the third level [1].

1.1 Definition

An epilepsy syndrome (ES) refers to a group of features that includes seizure types, EEG, and imaging features that tend to occur together. There are many well-known syndromes, such as childhood absence epilepsy, West syndrome, and Dravet syndrome, although it should be noted that there has never been a formal classification of syndromes. Therefore, it is important to note that epilepsy syndrome does not have a one-to-one correlation with an etiological diagnosis and serves a different purpose, such as guiding management [1].

2. Epilepsy syndrome diagnosis

2.1 When should one suspect an epileptic syndrome?

On analyzing the history, the following keys are to be identified for a syndromic diagnosis [1]:

Mixture of generalized and partial epilepsy; special seizure types i.e. temporal lobe epilepsy or myoclonic epilepsy; association with other impairments i.e. neurological impairments, mental retardation, other organ disorders (eyes, muscles spleen, etc.); seizures related to the times of eating, fasting, protein-rich meal; unexplained Status epilepticus; inefficacy or worsening with classical antiepileptic drugs; and paraclinical Findings.

2.1.1 Diagnostic approach to syndromic epilepsy

2.1.1.1 Disease course

One of the most important points that should be noted in the history of an epileptic patient is the *disease course*. Non-progressive course suggests a static nature of disorders like stroke, chromosomal diseases, perinatal hypoxia, etc. On the other hand, starting and tempered profiles in progressive disorders play three patterns:

Acute: The presence of abrupt and severe symptoms, along with periods of improvement and worsening, a connection to infections, fasting, or specific dietary habits, non-specific physical indications, and a positive reaction to symptomatic treatment, frequently indicates a deficiency in intermediary metabolisms, such as aminoacidopathies, organic acidemias, and fatty acid oxidation disorders.

Insidious onset: A gradual onset, persistent and progressive symptoms, and symptoms and signs that are independent of intervening events often suggest organelle disorders such as lysosomal storage disorders and peroxisomal disorders.

Episodic progression of symptoms: There are exceptions to this generalization. For example, Leigh's disease, which is an organelle disease, is characterized by a sudden onset of encephalopathy and an episodic course [2].

2.1.1.2 Extra-neural involvements

1. If a person has unusual physical characteristics in their fingers, face, spine, toes, extremities, or internal organs, it may indicate that these features developed before birth. Coarse facial features are often associated with mucopolysaccharidoses, GM1 gangliosidoses, mucolipidoses, and glycoprotein syndromes such as fucosidosis. Children with hyperhomocystinuria may have a Marfanoid habitus [2].

2. Skin and hair abnormalities can provide valuable information for diagnosing systemic diseases that affect the nervous system. For example:

   - A child with sparse, light-colored hair, hair loss, and recurring skin rashes, along with regression and seizures that do not respond to treatment, may have biotinidase deficiency;

   - A child with seborrheic dermatitis, hypopigmented kinky hair, epilepsy, and regression in early infancy is immediately diagnosed with Menkes disease;

   - *hypertrichosis* is a feature of mitochondrial disorders, especially in *SURF1*-positive Leigh disease.

   - A child has spastic paraplegia and leukoencephalopathy on an MRI, along with ichthyosis (a scaly skin condition), which may indicate Sjogren Larsson syndrome.

- Angiokeratomas, which are small, dark red or purple spots on the skin, can be observed in both Fabry's disease and fucosidosis.

- Cutaneous melanosis, which is an abnormal darkening of the skin, is another important clinical clue in patients with lysosomal storage disorders, particularly GM1 gangliosidosis.

- hyperpigmentation of the oral mucosa, genitals, and navel in a child with regression of milestones may indicate a diagnosis of adrenoleukodystrophy [2, 3].

3. Measurement of head circumference and velocity of growth is an important aspect of a clinical examination and can provide valuable diagnostic information. For example:

   - If a child has an abnormally large head (macrocephaly) and exhibits a startling response to sound, along with regression at around six months of age, may indicate a diagnosis of GM2 gangliosidosis.

   - Extreme irritability, incessant crying, opisthotonic posture, and regression are diagnostic clues to Krabbe disease.

   - In glutaric aciduria type 1, episodic regression occurs after febrile illnesses, especially mild diarrheal illnesses, together with macrocephaly and dystonia.

   - In a child with suspected leukodystrophy, a large head suggests a variety of diagnoses such as Canavans disease, Alexander disease, and megalencephalic leukodystrophy with subcortical cysts.

   - Macrocephaly can also be seen in another important late-onset metabolic disorder, L-2-hydroxyglutaric aciduria, in which there is evidence of leukoencephalopathy on MRI [2–4].

4. The eye is often referred to as a "window to the brain". This is because the eye is connected to the brain through the optic nerve, which carries visual information from the eye to the brain. By examining the eye, doctors can sometimes detect changes or abnormalities in the brain that may be indicative of certain medical conditions [2, 5].

   - *Ocular anterior chamber examination:* The main points to look for are the presence of cataracts, lens luxation, and corneal opacity. When children present with progressive extrapyramidal signs, it is important to look for the Kayser Fleisher ring to establish a diagnosis of Wilson's disease. The presence of lens dislocation in a child with refractory neonatal-onset epilepsy may indicate isolated sulfite oxidase deficiency or molybdenum co-factor deficiency. In contrast, lens dislocation in a child with mental retardation, behavioral disturbances, and Marfanoid habitus may suggest homocystinuria. Corneal opacity is a characteristic feature of cerebrotendinous xanthomatosis, mucopolysaccharidoses, and mucolipidosis type 4. In these disorders, corneal opacity may be associated with ptosis, oculomotor disorders, retinal degeneration, optic atrophy, and spastic atactic syndrome. MRI may reveal a thin corpus callosum

and variable degrees of hypomyelination. However, visceromegaly and skeletal manifestations are typically absent in these children.

- *Ocular posterior chamber examination:* Changes in the appearance of the optic nerve can be a sign of increased pressure in the brain, which may be caused by conditions such as a brain tumor or hydrocephalus. Retinitis pigmentosa, optic atrophy, papilledema, and cherry red spots. Pigment disorders of the retina often occur in diseases of the mitochondria, neuronal ceroid lipofuscinoses, and disorders of peroxisomal biogenesis. Cherry-red spots typically appear in lysosomal storage disorders such as Tay-Sachs disease, Niemann-Pick type C disease, and GM1 gangliosidosis. As a novel and non-invasive tool, Optic Coherence Tomography findings will evaluate papilledema in epileptic cases.

- *Ocular eye movement examination:* Certain eye movements and reflexes can provide clues about the functioning of the brainstem, which is responsible for controlling many vital functions such as breathing and heart rate. *Vertical supranuclear gaze palsy* may suggest Niemann Pick type C disease.

3. Etiologies of syndromic epilepsy

3.1 Structural

It is important for neurologists, particularly epileptologists, and those working on multidisciplinary epilepsy teams to recognize the link between structural brain abnormalities and epilepsy. Tumors, trauma, bleeding, abscesses, and encephalitis can be difficult to detect with conventional imaging methods [6]. In some cases, imaging with 3 T MRI and high-resolution CT of the skull base may be required to confirm temporal lobe sclerosis and encephaloceles, particularly in patients with nonlesional temporal lobe epilepsy (TLE). Treatment of drug-resistant TLE due to temporal lobe encephalocele and sclerosis is primarily surgical and most patients have a good outcome (postoperative Engel Class I).

Temporal lobe encephaloceles are increasingly recognized as a cause of epilepsy. Recent studies have found an association between temporal lobe encephalocele and IIH, suggesting that TLE may be an unusual manifestation or complication of IIH. It has been suggested that pulsatile forces in the cerebrospinal fluid (CSF) due to increased intracranial pressure can lead to the development of prominent arachnoid villi that form CSF pockets, leading to the formation of spontaneous CSF fistulas and encephaloceles [7].

Patients with temporal lobe epilepsy (TLE) and temporal lobe encephalocele have similar demographic characteristics as patients with idiopathic intracranial hypertension (IIH); including female dominance and high body mass index (BMI). Several studies have also shown a high prevalence of raised intracranial pressure (RAD-IH) in patients with TLE and temporal lobe encephalocele, including enlarged or empty sella, enlarged Meckel's cavity, optic nerve sheath distension, flattening of the posterior bulb, and transverse venous sinus stenosis. Other symptoms and signs of IIH, such as headache, visual disturbances, pulsatile tinnitus, and papilledema, are rare in patients with TLE and temporal lobe encephalocele. However, some patients with TLE and temporal lobe encephalocele have elevated cerebrospinal fluid (CSF) opening pressure greater than 25 cm H_2O, supporting an association with IIH [7–14].

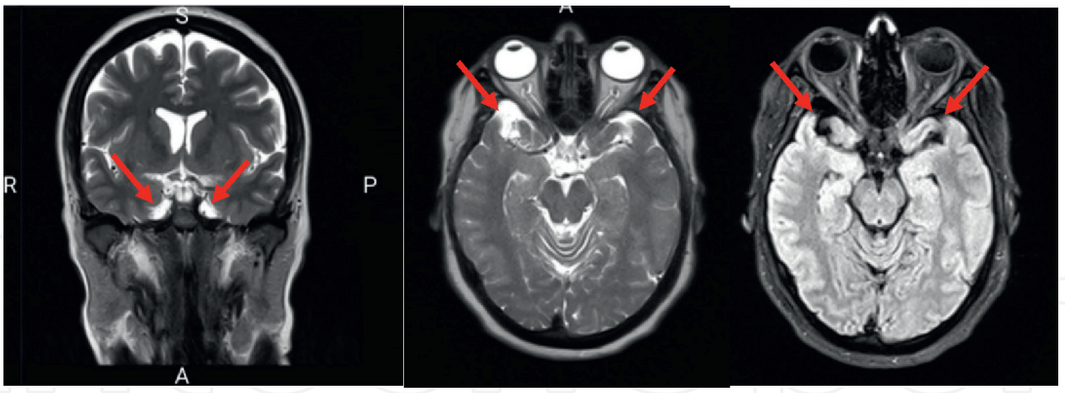

Figure 1.
Bilateral encephaloceles showing by red arrows in brain MRI (a) T2 weighted coronal cut; (b) T2 weighted axial cut at the same level; (c) T1 weighted axial cut at the same level (Bita Shalbafan courtesy).

In a large series of 474 patients examined over 5 years in a center for epilepsy surgery, temporal lobe encephalocele was identified in 25 (5.3%) patients. In these patients, the temporal lobe encephalocele was regarded as an epileptogenic focus in 48% of the cases. Temporal lobe encephaloceles are thought to cause mechanical irritation of the temporal lobes, and secondary changes such as inflammation and gliosis serve as a starting point for seizures. Most temporal lobe encephaloceles are asymptomatic and are discovered incidentally in patients with no history of seizures. However, in a small proportion of patients with drug-resistant temporal lobe epilepsy, temporal lobe encephaloceles associated with an anterior middle fossa defect (anteromedial and anteroinferior temporal lobe encephaloceles) appear to lateralize to the side of seizure onset, showing high concordance with studies including PET, scalp EEG and seizure semiology (**Figure 1**) [7–14].

3.2 Infectious diseases

Various infections of the central nervous system can cause both acute seizures and epilepsy. The pathogenesis and clinical presentation of seizure disorders can vary significantly depending on the infectious agent. The exact mechanisms underlying these differences are not well understood, but they appear to be at least partially related to factors such as the type of pathogen, the extent of cortical involvement, delays in treatment, and the host's inflammatory response.

Acute viral encephalitis can be caused by a variety of viruses, including herpes viruses, enteroviruses, paramyxoviruses, and arthropod-borne and zoonotic viruses. Some of the most common viruses associated with acute viral encephalitis include [15, 16]:

Herpes simplex virus type 1: This is the most commonly diagnosed sporadic encephalitis.

Enterovirus 71: This virus is associated with epidemic hand, foot, and mouth disease, aseptic meningitis, brainstem encephalitis, and myelitis.

Measles virus: This virus can cause acute post-infective encephalitis, subacute encephalitis, and subacute sclerosing panencephalitis.

West Nile virus: This virus is found in North America, Southern Europe, the Middle East, and West and Central Asia, and is associated with flaccid paralysis and Parkinsonian movement disorders.

Disease	Parasite	Transmitted by
Neurocysticercosis	*Taenia solium*	pork
Malaria	*Plasmodium falciparum*	mosquitoes
Toxoplasmosis	*Toxoplasma gondii*	cat
Schistosomiasis	*Schistosoma*	freshwater snail
Trypanosomiasis	*Trypanosoma*	tsetse fly

Table 1.
Seizure-induced parasitic infections.

Japanese encephalitis virus: This virus is found in Asia and is associated with flaccid paralysis and Parkinsonian movement disorders.

Rabies virus: This virus is transmitted by dogs, cats, and bats, depending on the location.

Other viruses that can cause acute viral encephalitis include varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, mumps virus, and tick-borne encephalitis virus. It is important to note that viral causes of chronic encephalitis, such as JC virus, are not included in this list. A thorough evaluation by a neurologist or other specialist is necessary to determine the underlying cause of encephalitis and develop an appropriate management plan.

It is important to note that while these parasitic infections can cause seizures, they are relatively rare in developed countries (**Table 1**) [15, 16].

3.3 Autoimmune diseases and paraneoplasia

Despite the high seizure frequency and propensity to develop status epilepticus (SE) in the acute stage of autoimmune encephalitis (AE), most patients with AE do not develop a long-term predisposition to seizures. This important concept was highlighted by the International League Against Epilepsy (ILAE) in 2020 when the Autoimmunity and Inflammation Taskforce proposed two main diagnostic entities: "acute symptomatic seizures secondary to AE" and "autoimmune-associated epilepsy". The latter occurs in a minority of cases and is often due to the development of structural abnormalities after the resolution of the inflammation (eg, mesial temporal sclerosis) or to a persistent antigenic trigger (eg, cancer in paraneoplastic cases). The amount of new information in this area over the last decade regarding clinical specifics, laboratory diagnostics, and treatment options has made it difficult for neurologists to target patients with AEs and seizures [17–21].

The predisposition to cause enduring seizures in autoimmune encephalitis is dependent on the mechanism that drives the immune response, ranging from a high predisposition in cytotoxic T cell-mediated encephalitis (intracellular antigens) to a moderate or absent predisposition in antibody-mediated encephalitis (surface antigens). Among the latter, the severity of the seizures and the likelihood of developing epilepsy vary according to the antigen. Additionally, all these disorders occur with a variable degree of inflammation that could have downstream effects on synaptic function, hyperexcitability, and epileptogenesis. Several autoimmune antibodies to: Glutamate/NMDA-NR1, Glutamate/AMPA-GluR3, Glutamate/NMDA-NR2, GABA-R, GAD-65, GLY-R, LGI1, VGKC, CASPR2, and β2 GP1, found in subpopulations of epilepsy patients. AMPA-GluR3B peptide antibodies as Glutamate receptor antibodies seem so far the most

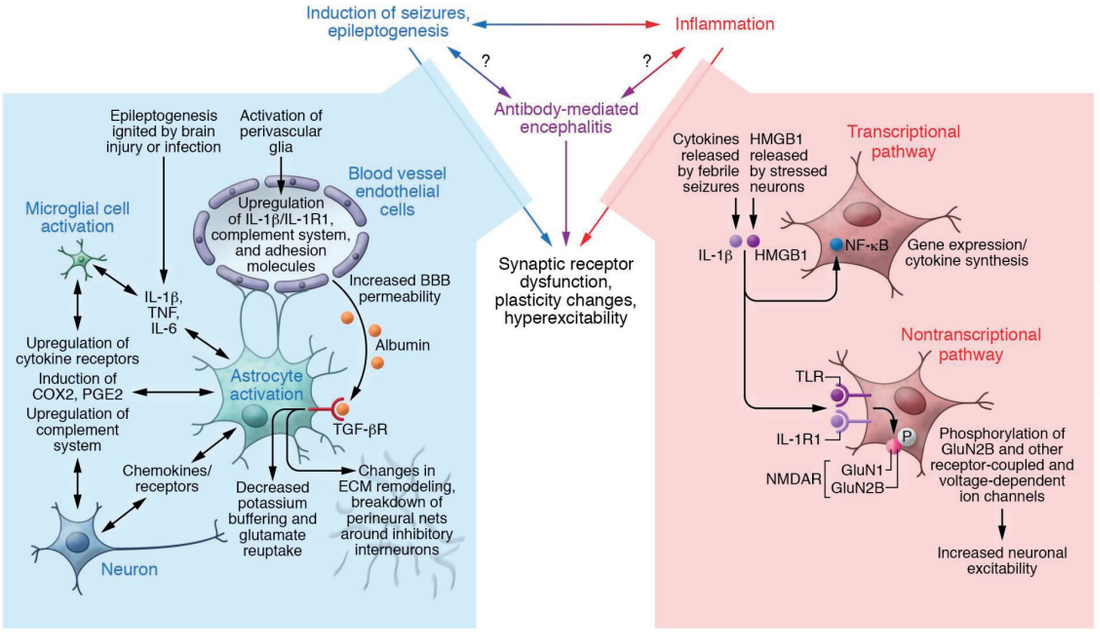

Figure 2.
Multiple inflammatory/innate immunity mechanisms triggered by seizures and epileptogenesis.

exclusive and pathogenic autoimmune antibodies in AE. They kill neural cells by three mechanisms: reactive-oxygen-species, excitotoxicity, and complement fixation, and facilitate and/or induce brain damage, seizures, and behavioral impairments. Also, the additional autoantibodies GABA-R, dopamine-R, Ach-R, adrenergic-R, and serotonin-R are present in various neurological diseases (**Figure 2**) [17–21].

From a clinical perspective, only a few seizure types are pathognomonic for an autoimmune etiology, including faciobrachial dystonic seizures (FBDS) and seizures originating in perisylvian (islet-opercular) regions. FBDS are very brief (<3 s) tonic muscle contractions in the arm and face, and more rarely in the leg. They are usually unilateral, but can also independently affect both sides asynchronously and occur up to 100 times a day, including during sleep. FBDS are thought to be pathognomonic of anti-LGI1 encephalitis, and their early detection (and consequent initiation of immunotherapy, particularly corticosteroids) can prevent the onset of cognitive dysfunction characteristic of the disease. Seizures with perisylvian semiology, including autonomic and somatosensory/viscerosensory symptoms, are not associated with a specific antibody but are often indicative of an immune-mediated etiology. A multicenter study found that autoimmune etiologies were more common than infection in NORSE (new-onset refractory status epilepticus), with autoimmune etiologies comprising 19% nonparaneoplastic and 18% paraneoplastic cases. These results suggest that autoimmune pathogenesis is much more likely in NORSE than viral infection. Therefore, after a thorough investigation of the infection, it is possible to consider NORSE as a potentially autoimmune epilepsy that requires active immunotherapy. A similar condition has been described in children, which is defined as febrile infectious epilepsy syndrome (FIRES). In these cases, the presence of a febrile episode between 2 weeks and 24 hours before the onset of RSE is required. Some authors argue that NORSE and FIRES are different entities. However, the two syndromes share many similarities and nowadays FIRES is considered a subcategory of NORSE (**Figure 3**) [17–21].

Timely identification of an autoimmune cause of seizures is crucial as it has relevant therapeutic implications. Several criteria and scoring systems for autoimmune

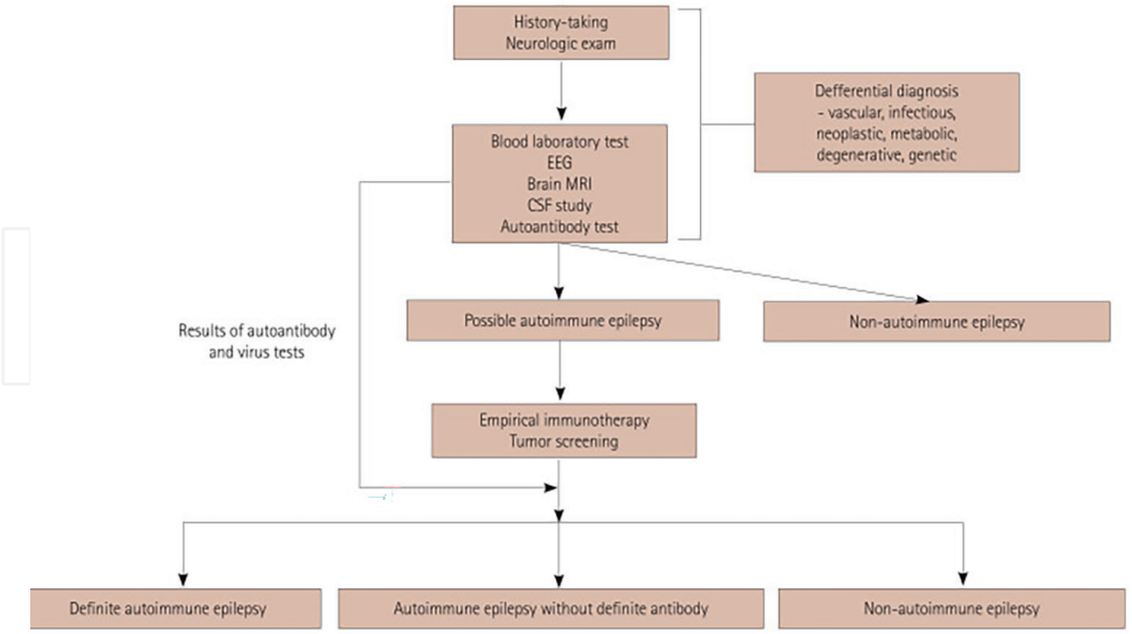

Figure 3.
The diagnostic approach to autoimmune epilepsy begins with a detailed history-taking and neurological examination. To exclude other etiologies of epilepsy, various diagnostic workups including blood laboratory tests, electroencephalography (EEG), brain magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) studies are performed. Empirical immunotherapy can be applied during the diagnostic tests. The final diagnosis is made based on the results of the tests and the response to immunotherapy. Blood laboratory tests may include autoimmune antibody panels, complete blood count, erythrocyte sedimentation rate, C-reactive protein, and liver and kidney function tests. EEG can help identify seizure activity and epileptiform discharges. Brain MRI can detect structural abnormalities and inflammation. CSF studies can detect inflammation and the presence of specific antibodies. Empirical immunotherapy may include corticosteroids, intravenous immunoglobulin, or plasma exchange. The response to immunotherapy can help confirm the diagnosis of autoimmune epilepsy.

seizures and epilepsy have been proposed, such as the Autoantibody Prevalence in Epilepsy Score (APE) and its subsequent revision (APE2), the Antibody Contribution to Focal Epilepsy Signs and Symptoms (ACES) score, and others. A clinician should be certain that the panel chosen includes antibodies for the suspected etiology (**Table 2**) and screen for antibodies associated with conditions that present similarly (ie, GQ1B, ANA, and TPO/thyroglobulin antibodies) [17, 18].

3.4 Inborn errors of metabolism (IEMs)

Although IEMs are a rare etiology in child and adult epileptic cases, these are important to recognize for several reasons: dramatic response to specific treatments; early treatment can stop disease progression in neural and extra-neural tissues; some antiepileptic drugs interfering with metabolic pathways may worsen the clinical condition; specific genetic counseling can be provided.

When a metabolic disease is suspected, the approach to metabolic investigations should be guided by the type of epilepsy, associated signs, and the presence or absence of mental retardation. In critical situations, such as an unexplained status epilepticus, ammonia measurement and search for porphyries should be mandatory. In other situations, simple examinations aimed at identifying treatable diseases should be seen as a priority. Metabolic investigations may include blood tests to assess electrolyte levels, glucose, liver and kidney function, and thyroid

Autonomic dysfunction: atrial bradycardia or sustained tachycardia, blood pressure labile, bradycardia, cardiac aystole, hyperhidrosis, orthostatic hypotension, ventricular tachycardia.	1
Brain MRI: consistent with limbic encephalitis (medial temporal T2/FLAIR signal changes)	2
Seizure or cognitive changes: rapidly progressive mental changes over 1–6 week period or new onset seizure (within 1 year of evaluation)	1
CSF findings consistent with inflammation: protein >50 mg/dL and lymphocytic pleocytosis >5 cells/dL, if total number of red blood cells is <1000 cells/dL	2
Facial dyskinesia or faciobrachial dystonia	2
Malignancy (excludes cutaneous basal cell carcinoma or squamous cell carcinoma)	2
Psychiatric symptoms (agitation, aggression, emotional lability)	1
Seizure refractory to medical treatment	2
Viral prodrome (low-grade fever, sore throat, rhinorrhea); scored only if there is no underlying malignancy	2

Note. An APE Score of ≥4 (max: 15) predicts detection of neural autoantibody in autoimmune epilepsy (sensitivity: 97.7%,; specificity: 77.9%) [17].
Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery.

Table 2.
Autoantibody prevalence in epilepsy score.

function. Urine tests may also be performed to assess for metabolic abnormalities. Genetic testing may be considered in patients with suspected inherited metabolic disorders. In patients with suspected mitochondrial disorders, muscle biopsy may be necessary to assess mitochondrial function. Magnetic resonance spectroscopy (MRS) can also be used to evaluate brain metabolism and detect metabolic abnormalities. It is important to note that metabolic investigations should be conducted in consultation with a metabolic specialist or neurologist with expertise in metabolic disorders, as the interpretation of results can be complex and require specialized knowledge (**Figure 4**) [2, 19].

To recognize the type of IEM clinical history needs to be analyzed considering the following points [2]:

3.4.1 Pattern of inheritance

- *Autosomal dominant traits* can be present in successive generations, although the level of expressivity can vary.

- *Autosomal recessive traits* are often not manifested in consecutive generations but may be present in siblings. Almost 90% of metabolic disorders are inherited in an autosomal recessive manner. Because of the little siblings, cases appear to be sporadic at times. A family history of unexplained neonatal or infant deaths should be obtained.

- *X-linked recessive* disorders manifest in male siblings, male first cousins, and maternal uncles, e.g. B. Fabry disease, X-linked adrenoleukodystrophy, and Lesch-Nyhan disease.

A maternal inheritance pattern suggests a mitochondrial disorder, which is caused by mutations in the mitochondrial DNA (mtDNA) that is inherited from the mother. It is important to note that mitochondrial disorders can also follow a Mendelian

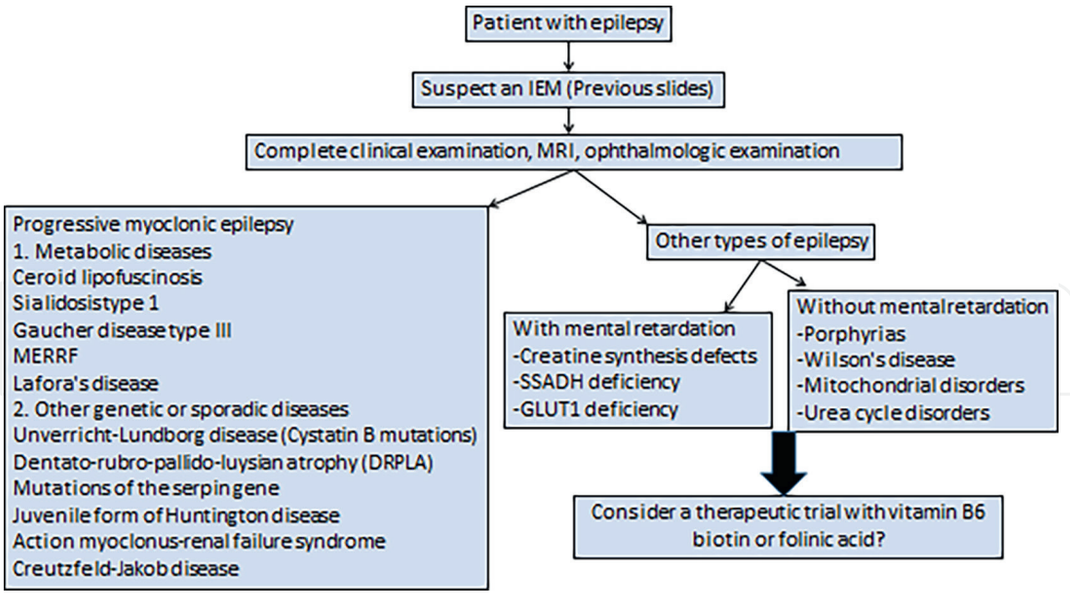

Figure 4.
Diagnostic approach in an epileptic patient in order not to miss an IEM summarize presumed hereditary predisposition critical problem of inherited stigma in some parts of the world causes us to prefer the idiopathic labeling to these epileptic cases instead of genetic names. Also, findings of many de novo mutations cannot confirm the pathogenicity of these genetic findings in both mild and severe epilepsies.

pattern of inheritance, such as autosomal dominant or recessive inheritance, depending on the specific mutation and the proportion of mutant mtDNA in the affected individual.

In some cases, an apparent autosomal inheritance pattern may mask a maternal inheritance. This can occur when a mutation in the mtDNA is present in both the mother and father, but the father's contribution of mtDNA to the offspring is much lower than the mother's. As a result, the offspring may appear to inherit the mutation in an autosomal dominant or recessive pattern, when in fact it is a mitochondrial disorder with maternal inheritance.

Therefore, when evaluating a patient with suspected mitochondrial disorder, it is important to consider both the maternal inheritance pattern and the possibility of Mendelian inheritance. Genetic testing, including mtDNA sequencing and analysis of nuclear genes involved in mitochondrial function, may be necessary to confirm the diagnosis and determine the mode of inheritance (**Table 3**) [2].

It is important to recognize that the clinical presentation and imaging features of the same disease can vary in different age groups. Therefore, it is essential to be familiar with the variable presentation of these disorders in different age groups to make an accurate diagnosis and develop an appropriate management plan. For example, Tay Sachs disease or infantile GM2 gangliosidosis typically presents with neuroregression and an exaggerated startle response to sounds. In contrast, the presentation of juvenile-onset GM2 gangliosidosis includes neuroregression, gait difficulty, ataxia, peripheral neuropathy, and psychosis. The classical early infantile Krabbe leukodystrophy presents with regression, irritable cry, and opisthotonic posturing, while juvenile onset Krabbe leukodystrophy presents with spastic paraparesis or visual impairment. In addition to the clinical presentation, the magnetic resonance imaging (MRI) findings can also vary in different age groups. For example, in early infantile Krabbe leukodystrophy, MRI typically shows diffuse white matter abnormalities, while in juvenile-onset Krabbe leukodystrophy, MRI may show focal white matter

Diagnosis	Onset	Seizure type	Nonepileptic clinical findings	Diagnostic evaluation
Glycine encephalopathy	Neonatal period to early infancy	Myoclonic jerks, infantile spasm	—	Elevated glycine on TMS and quantitative estimation of amino acids
Isolated sulfite oxidase/ Molybdenum cofactor deficiency	Neonatal period to early infancy	Refractory seizure	Presentation similar to hypoxic ischemia encephalopathy, facial dysmorphism, lens dislocation	Low serum uric acid, positive urine sulfite testing
Maple syrup urine disease	Neonatal period to early infancy	GTS	Encephalopathy, abnormal smell of the body and urine	Elevated branched-chain amino acids on TMS, urinary DNPH test-positive
Phenylketonuria	Early infancy to childhood	Infantile spasms,	Hypopigmented hair, abnormal smell of urine, microcephaly	Elevated phenylalanine on TMS/HPLC, positive ferric chloride, and DNPH test
Menkes kinky hair syndrome	Early infancy to childhood	Focal clonic seizures, infantile spasms, myoclonic seizures	Hypopigmented kinky and friable hair, hypotonia, seborrheic dermatitis	Low serum copper and ceruloplasmin levels, hair microscopy-pili Torti
Biotinidase deficiency	Early infancy	Infantile spasms, refractory myoclonic seizures	Alopecia, hypopigmentation of hair	Elevated C5-OH levels on TMS, elevated beta hydroxyl isovalerate, methyl citrate, and beta hydroxy propionate and lactate on urinary organic acid analysis, dramatic response to biotin
Progressive neuronal degeneration [Alpers disease/ polymerase gamma (POLG) related disorder]	Late infancy to early childhood	GTC, myoclonic jerks	Transient hemiplegia, fatal hepatic encephalopathy especially after sodium valproate use	Elevated liver enzymes, POLG1 genetic study,

Table 3.
Neurometabolic disorders with epilepsy as the main manifestation.

abnormalities. Therefore, a thorough evaluation by a neurologist or other specialist is necessary to make an accurate diagnosis and develop an appropriate management plan, taking into account the age of the patient and the variable presentation of the disorder in different age groups [2].

3.4.2 Key clinical symptoms and signs with special focus on sites of neuraxis

When evaluating a patient with a suspected neurological disorder, it is important to determine whether the primary symptoms and signs are related to gray matter

involvement, white matter involvement, behavioral or psychiatric manifestations, extrapyramidal system involvement, or peripheral nerve system involvement. Gray matter involvement can present with symptoms such as seizures, visual impairment, and cognitive decline. Examples of disorders that primarily involve gray matter include epilepsy, Alzheimer's disease, and Huntington's disease. White matter involvement can present with symptoms such as gait difficulty, abnormalities in tone (spasticity/hypotonia), and sensory deficits. Examples of disorders that primarily involve white matter include leukodystrophies, multiple sclerosis, and cerebral palsy. Behavioral or psychiatric manifestations can present with symptoms such as aggression, irritability, and anxiety. Examples of disorders that primarily involve behavioral or psychiatric manifestations include autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia. Extrapyramidal system involvement can present with symptoms such as dystonia, tremor, and choreoathetosis. Examples of disorders that primarily involve the extrapyramidal system include Parkinson's disease, Huntington's disease, and dystonia. Peripheral nerve system involvement can present with symptoms such as polyneuropathy and pes cavus. Examples of disorders that primarily involve the peripheral nerve system include Charcot-Marie-Tooth disease and hereditary neuropathies. Therefore, a thorough evaluation by a neurologist or other specialist is necessary to determine the primary symptoms and signs and develop an appropriate management plan based on the underlying pathology [2].

3.4.2.1 Association with extraneural impairments

It was explained in detail in part 2.1.1.2.

3.4.2.2 Progressive myoclonic epilepsy

This is a group of disorders characterized by a specific set of clinical features, electroencephalography (EEG) findings, and response to treatment. However, in some cases, the clinical presentation of epilepsy may not match with any classical ES. This is known as an atypical electro-clinical presentation. Atypical electro-clinical presentation can refer to a variety of features, including an unusual combination of seizure types, an unusual age of onset, or an unusual response to antiepileptic drugs. For example, a patient may present with a mixture of generalized and partial epileptic manifestations, such as the association of myoclonus and partial seizures in a given patient. In such cases, a thorough evaluation by a neurologist or other specialist is necessary to determine the underlying pathology and develop an appropriate management plan. This may include further diagnostic tests, such as brain imaging or genetic testing, to identify the cause of the atypical presentation. Treatment may involve a combination of antiepileptic drugs and other therapies, such as surgery or behavioral interventions, depending on the specific features of the atypical presentation. It is important to note that atypical electro-clinical presentation is relatively rare and may require specialized expertise to diagnose and manage. Therefore, referral to a specialist center or epilepsy center may be necessary in some cases (**Table 4**) [2].

3.4.2.3 Other red flags

Anti-epileptic drugs may exacerbate epilepsy or trigger a metabolic attack in patients with IEMs (**Table 5**) [20].

Diagnosis	Onset	Clinical features except seizure	MRI findings	Diagnostic evaluation
Neuronal ceroid lipofuscinosis	Infantile, late Infantile, juvenile adult onset	Rapidly advancing psychomotor retardation, ataxia, blindness, Retinitis Pigmentosa, optic atrophy	cerebral and cerebellar atrophy with periventricular signal changes	Giant somatosensory evoked potential, electron microscopy of axillary skin shows characteristic inclusion
Cherry red spot myoclonic syndrome	Late childhood to adolescence	GTCS, ataxia, cherry red spot	Nonspecific findings	Giant somatosensory evoked potential, Bone marrow storage cells
Myoclonic epilepsy ragged red fiber (MERRF) syndrome	Late childhood to adolescence and adulthood	Ataxia, intention tremor, Muscular weakness, deafness, optic atrophy	Nonspecific findings	Elevated lactate,Ragged red and blue fibers in muscle biopsy
Nieman Pick type C disease	Late childhood	Ataxia, cataplexy, supranuclear vertical gaze palsy, splenomegaly	Cerebellar atrophy	Bone marrow examination for storage cells,genetic testing
Gaucher disease type III	7–10 Y/O	psychomotor retardation, splenomegaly, osseous signs	Nonspecific findings	Glucocerebrosidase enzyme activity estimation by gottery test, bone marrow examination for storage cells
Late-onset GM2 gangliosidosis	4-10Y/O	Ataxia cherry red spots	Nonspecific findings	serum hexoseaminidase levels

TMS, Tendom Mass Spectroscopy; HPLC, High Performance Liquid Chromatography; MRS, Magnetic Resonance Spectroscopy.

Table 4.
Progressive myoclonic epilepsy syndromes.

Disease	Drugs that may exacerbate epilepsy or trigger a metabolic attack
Progressive myoclonic epilepsy (not specific to IEMs)	phenytoin, carbamazepine, gabapentin, vigabatrin, Tiagabine, lamotrigine
GLUT-1 deficiency	Diazepam, phenobarbital
SSADH deficiency	Valproate
Porphyrias	Valproate, lamotrigine, carbamazepine, phenytoin, topiramate
Urea cycle disorders	Valproate
Mitochondrial cytopathies	Valproate

Table 5.
List of IEMs that may be exacerbated by anti-epileptic drugs.

3.4.3 Paraclinic

Pattern of white matter abnormalities on magnetic resonance imaging (MRI) is one of the most important tools in the diagnosis of specific IEM types (**Figure 5**) [3]:

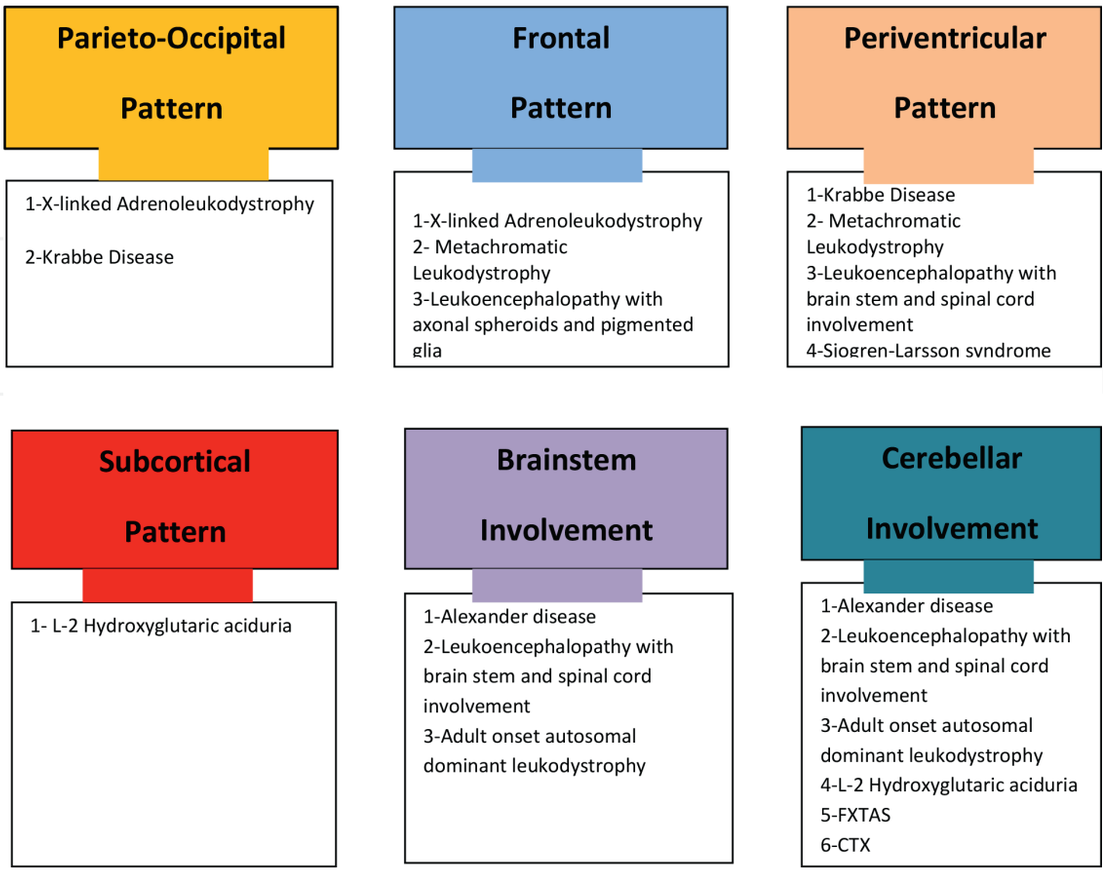

Figure 5.
Patterns of white matter abnormalities on magnetic resonance imaging (MRI) in IEM.

Abnormalities on *proton magnetic resonance spectroscopy*: for instance, creatine deficiency or increased in lactate in Mitochondrial disorders.

Electroencephalogram showing slowing of the background activity or photo-paroxysmal responses during the photic intermittent stimulation at low frequencies (1–6 H).

3.4.4 Treatable IEMs

When investigating a patient with refractory epilepsy or unexplained status epilepticus, it is important to consider the possibility of treatable diseases [20].

The following investigations may be considered:

1. Glucocerebrosidase activity: This test can help diagnose Gaucher disease, a rare genetic disorder that can cause seizures and other neurological symptoms.

2. Blood copper and ceruloplasmin: These tests can help diagnose Wilson's disease, a rare genetic disorder that can cause seizures and other neurological symptoms.

3. Blood and urine creatine (or proton magnetic resonance spectroscopy): These tests can help diagnose creatine deficiency syndromes, a group of rare genetic disorders that can cause seizures and other neurological symptoms.

4. Blood and CSF glucose (with calculation of the blood/CSF ratio): These tests can help diagnose hypoglycorrhachia, a condition in which the glucose level in the CSF is lower than expected. This can be caused by a variety of conditions, including infections, tumors, and metabolic disorders.

5. CSF lactate and search for mitochondrial disorders: These tests can help diagnose mitochondrial disorders, a group of rare genetic disorders that can cause seizures and other neurological symptoms.

6. In cases of refractory epilepsy or unexplained status epilepticus, a simple therapeutic trial with vitamin B6 (250 mg/day), biotin (10–300 mg/day), and folinic acid (25–50 mg/day) for several days or weeks may be considered. These vitamins can help improve seizure control in some patients with certain genetic disorders, such as pyridoxine-dependent epilepsy or biotinidase deficiency. It is important to note that these investigations should be conducted in consultation with a neurologist or other specialist with expertise in metabolic disorders, as the interpretation of results can be complex and require specialized knowledge [20].

4. Conclusion

When evaluating a patient with a suspected neurological disorder, the age at onset of symptoms is an important factor to consider. If the patient has a baseline developmental delay, the age at onset of neurological symptoms or regression is regarded as the age of onset.

It is useful to classify neurological disorders into broad groups based on the age at onset. For example, infancy is typically defined as the period from 1 to 12 months of age, while the late infantile/early juvenile onset period is from 1 to 5 years of age. The early infantile, late infantile/early juvenile, and late childhood periods are from 0 to 2 years, 2 to 6 years, and 6 to 12 years, respectively.

This classification can help guide the diagnostic workup and management of the patient. For example, certain neurological disorders, such as infantile spasms, are more common in the early infantile period, while others, such as Rett syndrome, typically present in the late infantile/early juvenile period.

In addition to the age at onset, other factors such as the pattern of inheritance, family history, and clinical features can also help narrow down the differential diagnosis and guide the diagnostic workup. A thorough evaluation by a neurologist or other specialist is necessary to make an accurate diagnosis and develop an appropriate management plan.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Bita Shalbafan
Neurologist, Tehran, Iran

*Address all correspondence to: b-shalbafan@alumnus.tums.ac.ir

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