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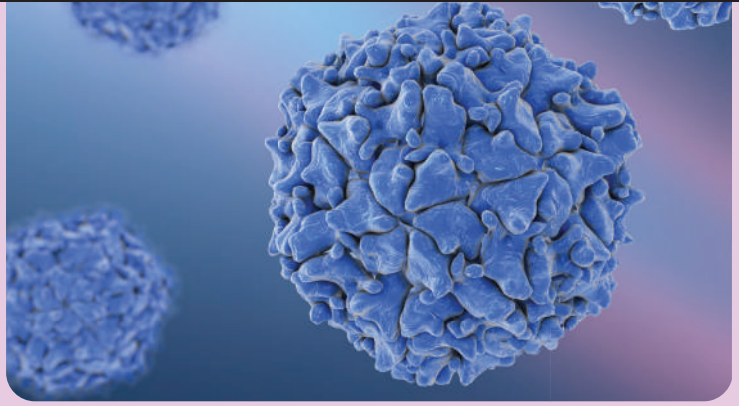


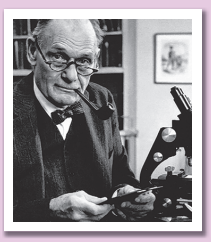
DISEASE HISTORY

Poliomyelitis

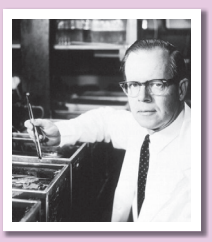
Polio is a highly infectious disease, mostly affecting young children, that attacks the nervous system and can lead to spinal and respiratory paralysis and in some cases death. Though Polio has existed since prehistoric times, the first known clinical description of polio was given by British doctor Michael Underwood in 1789 and it was formally recognized as a condition in 1840 by German physician Jakob Heine. By the mid - 20th century, the poliovirus could be found all over the world and killed or paralysed over half a million people every year. With no cure and epidemics on the rise, there was an urgent need for a vaccine.

A breakthrough occurred in 1949 when poliovirus was successfully cultivated in human tissue by John Enders, Thomas Weller and Frederick Robbins. Their pioneering work was recognized with the 1954 Nobel Prize. Not long afterwards, in the early 1950s the first successful vaccine was created by US physician Jonas Salk. Salk's inactivated polio vaccine (IPV) was licensed on 12 April 1955. A second type of polio vaccine; the oral polio vaccine (OPV) was developed by physician and microbiologist Albert Sabin. Sabin's vaccine was live - attenuated and could be given orally. The ease of administering the oral vaccine made it the ideal candidate for mass vaccination campaigns. In 1988, the World Health Assembly passed a resolution to eradicate polio - the Global Polio Eradication Initiative (GPEI) was launched. National Immunization Days were coordinated in 19 European and Mediterranean countries in 1995 and in 23 African countries in 2004. By 1994, polio had been eliminated from the Americas and by 2000 the Western Pacific was polio free. WHO's South-East Asia region was certified polio-free in 2014, the African region in 2020.

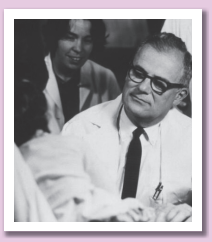
If a population is adequately immunized, it will be protected against both wild and vaccine-derived polioviruses.



John Enders
(February 10, 1897- September 8, 1985)



Thomas Huckle Weller
(June 15, 1915-August 23, 2008)



Frederick Robbins
(August 25, 1916-August 4, 2003)

Reference : https://www.who.int/

Chickenpox

Chickenpox is a very contagious infection caused by the *varicella zoster* virus. Chickenpox can affect anyone at any age. Chickenpox is more common in children. When adults catch chickenpox, they usually have a more severe illness and can take longer to get better. Most people with chickenpox have mild symptoms and get better quickly. Chickenpox can be more dangerous for some groups of people including pregnant women, people with weakened immune systems such as patients receiving chemotherapy & babies.

The main symptom of chickenpox is an itchy red rash. During the illness, the rash turns into fluid-filled blisters that burst and crust over. The infected person may also have fever or headache or can feel generally unwell. Symptoms usually start about 2 weeks after being around someone with chickenpox. They can continue for between 10 days and 3 weeks. A chickenpox rash starts with small, itchy red spots. Chickenpox is very contagious. Anyone is likely to catch chickenpox if the person isn't immune and come into contact with an infected person. Immunity can be achieved by vaccination and by having been infected previously.

The chickenpox virus is spread in two ways:

- Before the rash appears, the virus spreads through cough droplets that can travel through the air. This means that an infected person can spread chickenpox before they know that they are sick.
- Once the rash has developed, the virus can be spread through contact with the fluid in the blisters.

After being infected, it is recommended to stay home until the person is no longer contagious. Chickenpox is no longer contagious once all the blisters are crusted over. Chickenpox is usually diagnosed by a doctor through examination and collecting history of recent contact with anyone who has chickenpox and about vaccination history. In some cases, tests on fluid from your blisters may be done to confirm.

There is no specific treatment for chickenpox. Most people with chickenpox have mild symptoms and get better quickly, but chickenpox can still be uncomfortable. Chickenpox blisters can be very itchy. It can be hard to avoid scratching them especially for children. However scratching can increase the risk of infection and leave scars. Some people find it helpful to keep their fingernails short to make scratching more difficult. There are some other ways to ease symptoms -

- Using soothing lotions and antihistamines to reduce itching
- Keeping hydrated with water and other fluids
- Getting plenty of rest

In some cases, doctors may prescribe:

- Antibodies to reduce chance of becoming infected
- Antivirals to reduce the severity of the illness
- Soothing lotions and antihistamines to reduce itching
- Paracetamol to lower fever

Antibiotics will not help to get better because chickenpox is caused by a virus not bacteria. The best way to prevent chickenpox is through vaccination. The chickenpox vaccine is not advised during pregnancy, so it's better to get the vaccine before you get pregnant.

Reference: https://www.healthdirect.gov.au/

REVIEW ARTICLE

Neonatal seizures

INTRODUCTION

Neonatal seizures are defined as seizures occurring within 4 weeks after birth in full-term infants or within 44 weeks of postmenstrual age in preterm infants. The estimated incidence of these seizures is 2.29 cases per 1000 live births. Higher rates have been reported among preterm neonates than among full-term neonates (14.28 cases per 1000 vs 1.10 per 1000). The International League against Epilepsy (ILAE) has developed a diagnostic framework to classify neonatal seizures, which facilitates the use of common terminology and assists clinicians in making treatment decisions. Most neonatal seizures are transient and result from acute metabolic disturbances, infectious processes, or acute focal cerebral lesions. Such seizures are considered to be provoked. In full-term neonates, the most common cause of provoked seizures is hypoxic ischemic encephalopathy, followed in frequency by stroke and infection. In preterm neonates, the most common cause is intraventricular hemorrhage. Identifying the provoking event is essential for determining management.

Provoked seizures are not considered to be epilepsy which is defined as two or more unprovoked seizures and provoked seizures typically do not require long-term treatment with antiseizure medication. Neonatal epilepsy syndromes, which are uncommon, frequently have genetic causes and unlike provoked seizures, some of these syndromes require long-term treatment.

Clinical Presentation

Neonatal seizures start focally but can spread to involve the entire body. Seizures that begin in a generalized fashion are rare. Clinical seizures in neonates can be difficult to recognize because convulsive movements in babies are often complex, irregular or subtle. Because some seizures have only an electroencephalographic (EEG) component, the ILAE has emphasized the importance of EEG as essential for the identification of neonatal seizures. To address the limited availability of EEG in some settings, the Brighton Collaboration has proposed a scheme with five levels of diagnostic certainty that can guide treatment decisions if EEG is not available (Table 1).

- A clinical event that occurs simultaneously with a seizure pattern on continuous EEG recording provides the highest level of certainty that the event is truly a seizure and requires treatment (level 1).
- When a suspected event has a focal clonic feature (rhythmic focal jerking) or tonic feature (prolonged extension of the limbs) with or without EEG corroboration, treatment is also considered to be justified (level 2).

- If there has been an event that could be a seizure but is not focal, clonic or tonic and EEG is not available, treatment may be considered, but there is no clear guidance (level 3).
- Levels 4 (suspected seizure) and 5 (not a seizure) are self-explanatory and treatment is not required.

The same approach can be applied to single or multiple seizures.

A systematic review has suggested that clinical seizure types are usually associated with specific underlying causes. For example

Several common nonepileptic motor phenomena may be difficult to differentiate from seizures in neonates. Tremor, jitteriness and some myoclonic movements can be mistaken for seizures. They can occur without obvious cause or as symptoms of drug withdrawal, electrolyte abnormalities, hypoglycemia or infection. They do not have EEG correlates and are not seizures. If EEG is not available, the mentioned levels of diagnostic certainty can be used to assess the likelihood that a paroxysmal movement is a seizure. A common self-limiting neonatal condition, benign neonatal sleep myoclonus, is characterized by myoclonic events that occur during sleep, with a normal EEG. Neonatal hyperekplexia is a rare disorder of muscle rigidity, exaggerated startle reaction and nocturnal myoclonus, with a normal EEG and is also not an epilepsy syndrome. The attacks can be stopped by the Vigevano maneuver, consisting of forced flexion of the head and legs toward the trunk.

Table 1. Levels of Diagnostic Certainty

Level	Definition	Course of Action
Level 01: Definite Seizure	Suspected seizure with a continuous EEG correlate	Treat
Level 02: Probable seizure	Suspected seizure with an amplitude integrated EEG correlate or clinically assessed focal or tonic seizure	Treat
Level 03: Possible seizure	Clinical seizure other than focal tonic or clonic	Consider treatment
Level 04: Suspected seizue	Insufficient evidence to meet seizure criteria	Do not treat
Level 05: Not a seizure	Movement determined by EEG no to be a seizure	Do not treat
Seizures defined as definite or probable should be managed with antiseizure medication. If electroencephalography (EEG) is not avaible the clinician can		

- Focal clonic seizures usually signify a cerebral infarction and the need for cranial imaging to confirm the diagnosis.
- Tonic seizures are seen mainly with hypoxic ischemic encephalopathy but also with metabolic disorders, channelopathies, vascular disorders or cortical malformations. When the presentation includes myoclonic seizures (sudden, brief, irregular limb contractions), metabolic disorders such as hypoglycemia or hyponatremia, amino acid disorders or other inborn errors of metabolism are usually responsible.
- Sequential seizures are defined by the occurrence of more than one seizure type during an episode and are often genetically determined.
- Epileptic spasms (sudden flexion, extension, or mixed flexion with extension of the proximal and truncal muscles) also suggest genetic causes.
- Autonomic seizures are characterized by alterations in cardiovascular, vasomotor or respiratory patterns and are typically observed in neonates with hypoxic ischemic encephalopathy or intracranial hemorrhage.

Evaluation of Neonatal Seizures

The initial steps in managing neonatal seizures are to stabilize cardiovascular and respiratory function and then to identify the cause of the seizures. Treatable medical abnormalities such as hypoglycemia and electrolyte disorders (e.g., hyponatremia) can be rapidly detected and corrected, usually leading to cessation of seizures without the need for antiseizure medication. EEG monitoring should be initiated as early as possible to establish the presence of seizures because some types of seizures tend to peak in incidence and severity within the first 24 hours, particularly those due to hypoxic ischemic encephalopathy (Figure 1).

Perinatal, birth and family histories can provide clues to the underlying cause of seizures. For example some seizures such as those due to nonketotic hyperglycinemia begin prenatally and women may describe episodes of frequent, continuous, rhythmic jerking of the fetus. Certain examination findings also suggest specific causes of seizures: microcephaly may indicate cerebral dysgenesis, genetic abnormalities or congenital infection; macrocephaly may be due to structural or genetic abnormalities; dysmorphic features suggest cerebral dysgenesis, often due to a genetic abnormality; neurocutaneous stigmata are indicative of specific disorders such as tuberous sclerosis or neurofibromatosis; rash suggests infection or incontinentia pigmenti; and congenital heart disease is associated with perinatal stroke.

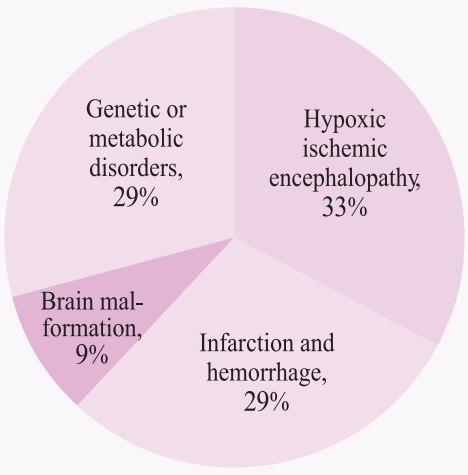


Figure 1. Causes of Acute Reactive Seizures in Term Neonates

When lumbar puncture is performed, saving cerebrospinal fluid (CSF) for possible additional studies is good practice. Figure 2 outlines a proposed diagnostic pathway that leads to the possible causes of seizures, and Table 2 provides a suggested evaluation for confirming each of several common causes.

A thorough evaluation might include screening for neonatal infection; toxicologic testing; metabolic testing for organic acidemias, urea cycle defects and fatty acid oxidation defects (which may include amino acid levels, ammonia, lactate, pyruvate, very-long-chain fatty acids, urine, organic acids, biotinidase, pipecolic acid and pyridoxal- 5- phosphate); and examination of the placenta for pathological changes. If an infectious cause is suspected, serum and cerebral spinal fluid cultures are generally obtained quickly and antimicrobial treatment is promptly initiated. If the neonate's condition is not sufficiently stable for a lumbar puncture, empirical treatment for meningoencephalitis is often appropriate.

If seizures continue despite the administration of conventional antiseizure medication, a pyridoxine challenge may be attempted since the rare condition known as pyridoxine - dependent developmental and epileptic encephalopathy

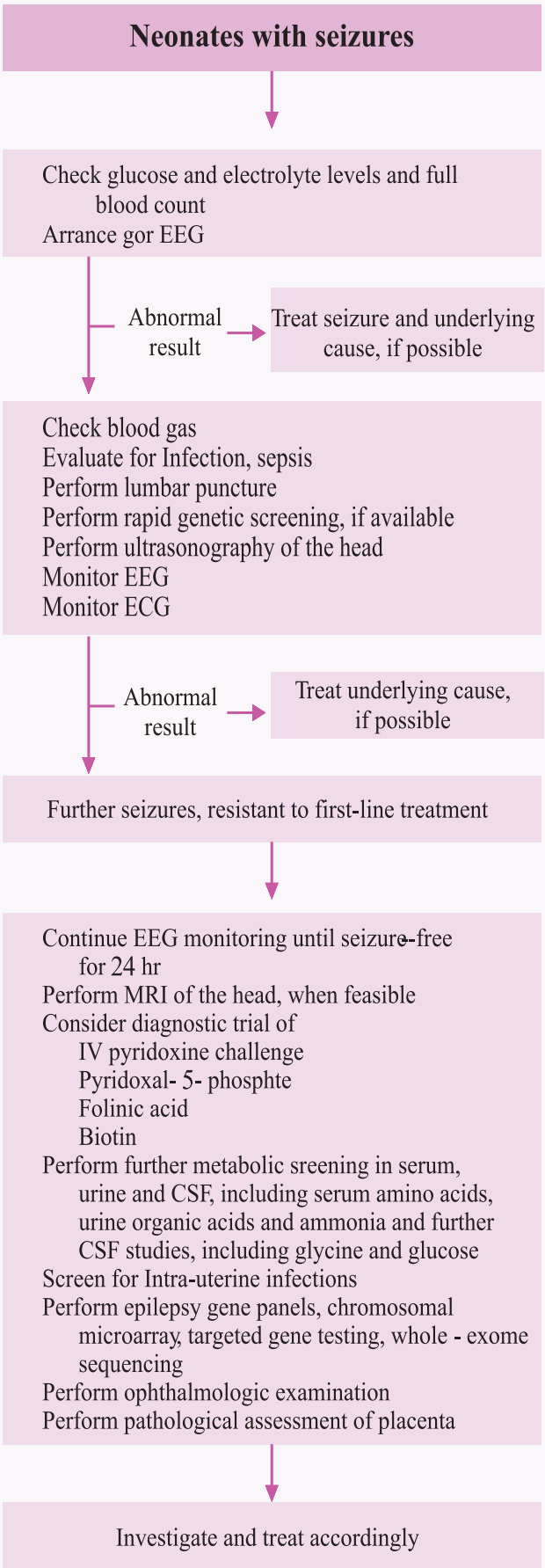


Figure 2. Proposed Diagnostic Process for Neonatal Seizures

responds to pyridoxine as discussed below. This diagnosis is uncovered by intravenous administration of 100 mg of pyridoxine followed by 30 mg of pyridoxine per kilogram of body weight per day administered intravenously or orally in two divided doses for 3 to 5 days with EEG monitoring of the response. Close cardiopulmonary monitoring during the infusion is recommended since there is a risk of apnea with intravenous pyridoxine. If a clear response is observed, pyridoxine administration is continued throughout the patient's lifetime.

Conventional 20-channel EEG or if that is unavailable, amplitude - integrated EEG may be used to diagnose neonatal seizures. Amplitude - integrated EEG is a single or double channel EEG recorded by three to five electrodes attached to the scalp. It is readily available as a bedside test, is easy to apply with either small-needle or adhesive electrodes and can be interpreted by neonatologists. However, amplitude - integrated EEG is less sensitive and less specific than conventional EEG for seizure detection because the limited number of electrodes makes it difficult to detect infrequent, brief and low-amplitude seizures. Amplitude - integrated EEG detected up to 38% of 851 seizures in one study. Continuous and video EEG monitoring, typically performed for at least 1 hour is a more accurate way to detect seizures than a single EEG recording. Continuous EEG monitoring is suggested until the neonate has been seizure-free for 12 to 24 hours. When EEG is not available, antiseizure treatment can be initiated by determining on the basis of the levels of diagnostic certainty described above, the likelihood that clinical events are seizures. Neonates may be transferred to a neonatal intensive care unit or to a facility with EEG capability, if that testing is not readily available. Neuroimaging is considered to be essential in the detection of possible structural abnormalities in neonates with seizure. Ultrasonography of the head is a first-line test because of its ease of use and accessibility at the bedside for acutely ill neonates who cannot be transported elsewhere. Ultrasonographic assessment has high sensitivity (100%) and specificity (93.3%) for detecting intraventricular hemorrhages with ventricular enlargement but the sensitivity is lower in the case of normal size ventricles or small cerebellar or extraaxial hemorrhages. Additional imaging with axial computed tomography or preferably, magnetic resonance imaging (MRI) of the head can be performed when feasible. Should a stroke be suspected on the basis of clinical features, magnetic resonance angiography and venography may be indicated as part of the assessment. Genetic testing is considered if there is no clear structural explanation for seizures such as stroke, hemorrhage or infection or if they are sequential seizures, epileptic spasms or tonic seizures. Although rare, some syndromes previously thought to be acquired as a result of perinatal insults have been found to be due to inherited or de novo pathogenic genetic variants. Therefore, clinicians are now testing more of their neonatal patients with undiagnosed seizures for genetic disorders and increasingly identifying these causes. Available genetic testing includes epilepsy gene panels, chromosomal microarray, targeted gene testing and whole exome sequencing. Knowledge of the role that genetics plays in epilepsy is rapidly evolving with increasing numbers of pathogenic variants identified as contributing to phenotypic epilepsy syndromes. Furthermore, pathogenic variants with strikingly different epilepsy syndromes occur within the same genotype.

Table 2: Workup for Acute Provoked Neonatal Seizures.*

Urgent Evaluation	Suspected HIE	Suspected Infection	Suspected Stroke	Suspected Metabolic Disorder
Obtain immediate laboratory measurements including glucose, electrolytes, and full blood count; confirm with EEG or amplitude - integrated EEG	Check birth history and Apgar score; screen for other causes, depending on clinical scenario; assess need for therapeutic hypothermia	Obtain blood cultures and TORCH titers; CSF studies: glucose and protein, cell counts, PCR assay for HSV, culture; pathological assessment of placenta	Imaging: MRI with diffusion-weighted imaging; evaluated for cause (e.g., thrombophilia or vascular or cardiac cause); echocardiagram; patho-logical assessment of placenta	Screen for other metabolic abnormalities (screen includes amino acids, ammonia, lactate, pyruvate, very-long-chain fatty acids, urine, organic acids, biotinidase, pipecolic acid, pyridoxine, pyridoxal - 5 - phosphate); opthalmologic evaluation)

*CSF denotes cerebrospinal fluid, HIE hypoxemic ischemic encephalopathy, HSV herpes simplex virus, PCR polymerase chain reaction, MRI magnetic resonance imaging and TORCH toxoplasmosis, other (syphilis, varicella, mumps, parvovirus, human immunodeficiency virus and Zika), rubella, cytomegalovirus and HSV.

Treatment of Acute Symptomatic Seizures

It is a generally accepted principle that all neonatal seizures with both clinical and EEG correlates and those with only EEG evidence should be treated. However, there are limited data from randomized, controlled trials to inform treatment decisions and medications are frequently used off label. The ILAE recently provided guidelines for the management of neonatal seizures on the basis of a systematic review, a meta-analysis and expert-based consensus. Medications used in the acute care setting are typically limited to intravenous formulations. The ILAE recommends phenobarbital as the first-line antiseizure medication, regardless of the cause (e.g., hypoxic ischemic encephalopathy, stroke, hemorrhage, or genetic causes). The Levetiracetam versus Phenobarbital for Neonatal Seizures (NEOLEV2) study, a small, phase 2b, randomized, controlled trial, showed that phenobarbital was more effective than levetiracetam at 24 hours for the treatment of neonatal seizures. Potential adverse effects of antiseizure medications on the developing brain are a concern. However, the risk is generally considered to be outweighed by the consequences of uncontrolled seizures. It is nevertheless important to discuss the possible cause of seizures and treatment options with the family as well as the potential duration of treatment on the basis of the neonate's response. The goal of treatment is seizure cessation. If the neonate does not have a response to the first antiseizure medication; phenytoin, levetiracetam, midazolam or lidocaine may be used as second-line intervention. However, there is limited evidence regarding the best medication to be used after phenobarbital has failed to control the disorder and there are no official guidelines for selecting such a medication or determining the dose. Practice has differed among institutions. Table 3 provides approximate antiseizure medication doses derived from the literature. For neonates with a cardiac disorder, levetiracetam is suggested as a potential second-line treatment over phenytoin because it is associated with fewer cardiac arrythmias and less potential cardiac toxicity. If conventional antiseizure therapies fail, one can consider trials of pyridoxine,

Table 3. Approximate Doses of the Main Antiseizure Medications for the Treatment of Neonatal Seizures.*

Medication	Loading Dose†	Maintenance Dose†	Comments
Phenobarbital	20 mg/kg of body weight; second loading dose, if required: 10-20 mg/kg, administered intravenously	5 mg/kg body weight per day, administered intravenously or orally	FDA-approved; enhances GABA inhibitory activity
Phenytoin	20 mg/kg of body weight; administered intravenously over 30-min period	5 mg/kg of body weight per day, administered intravenously in two divided dose, adjusted according to response and plasma concentration	off label use; voltage - gated sodium - channel blocker
Levetiracetam	20 mg/kg of body weight; administered intravenously; second loading dose, if required: 20 mg/kg	40-60 mg/kg of body weight per day, adminstered intravenously, or given orally in three divided dose	of- label use; binds to SV2A and impedes synaptic vesicle traffiking
Midazolam	0.05-0.15 mg/kg of body weight	1 µg/kg body weight per minute (60 µg/kg per hour), administered as a continuous infusion, increase in steps of 1 µg/kg per minute; maximum dose: 5 µg/kg per minute	of- label use; GABA agonist
Lidocaine	2 mg/kg of body weight, administered intravenously over 10-min period	7 mg/kg of body weight per hour, administered intravenusly for 4 hr, then 3.5 mg/kg per hour for 12 hr, then 1.75 mg/kg per hour for 12 hr and then stopped	of- label use; voltage - gated sodium- channel blocker

*Information on dose is from Dehkharghani, 12 Sharpe et al., 12 Van Den Broek et al.,15 Pisano et al.,16 Castro Conde al.,17 Sands et al.,18 Favie et al.,19 and Pressler et al.3 Other agents that may be used, depending on the clinical presentation, family history, laboratory tests, and EEG findings, include pyridoxine, pytridoxal5-phosphate, and depending on the clinical presentation, family history, laboratory tests,
y-aminobutyric acid type A, and SV2A synaptic vesicle protein 2A.
† Opinions about dosing vary and the doses shown should be taken as approximate values.
‡ Higher doses of phenobarbital may be given with careful cardiorespiratory monitoring.

pyridoxal phosphate and folinic acid to correct uncommon vitamin-responsive epilepsies. Therapeutic hypothermia for 72 hours is now used routinely for term and near-term infants with moderate - to - severe hypoxic ischemic encephalopathy in an effort to ameliorate the brain injury and improve later developmental outcomes. The ILAE found that there was weak evidence, but agreement among experts, that therapeutic hypothermia may reduce the seizure burden in neonates with hypoxic ischemic encephalopathy.

The consensus based recommendation is to stop the antiseizure medication only after all provoked seizures (both seizures for which there is clinical and EEG evidence and those for which there is only EEG evidence) have ceased, regardless of the MRI or EEG findings. However, this recommendation does not apply to neonatal-onset epilepsy syndromes, described below, because at least one type is likely to remit spontaneously and the other main type is typically resistant to medications. The recommendation comes from a nine - center, prospective, observational study of neonates with acute symptomatic seizures. The study considered the cause of the seizures, gestational age, status with respect to therapeutic hypothermia, EEG evidence of severity, the number of days on which EEG-confirmed seizures occurred and findings on neurologic examination at discharge. It was further found that discontinuing medication in patients with provoked seizures that had stopped before discharge was not associated with an increased risk of postneonatal epilepsy and did not alter the risk of functional disability at 2 years of age. The recurrence of seizures was not associated with medication withdrawal.

Neonatal Epilepsy Syndromes

The ILAE recently provided a position statement on the overall classification and definition of neonatal epilepsy syndromes. To some extent, these definitions incorporate previously recognized syndromes and are meant to facilitate prognostic and treatment recommendations. They can be divided into two broad categories: self-limited epilepsies, which in turn have two subcategories and developmental and epileptic encephalopathies. Developmental and epileptic encephalopathies are defined by intractable seizures associated with developmental impairment or regression often due to an underlying cause (which is likely to be genetic, structural, or metabolic). The self-limited neonatal epilepsy syndromes are due to pathogenic variants, either familial or de novo, most commonly in KCNQ2 and less commonly in KCNQ3. The typical self-limited epilepsy syndrome begins between 2 and 7 days after birth and remits after 6 months. Clues to this diagnosis are a family history of seizures and focal and tonic seizures at the onset of an episode but the syndrome may sometimes include focal clonic, tonic or sequential manifestations. Sodium-channel blockers are used when seizures are due to loss-of function KCNQ2 and KCNQ3 variants. Neuroimaging, genetic testing and metabolic studies show an underlying cause in up to 80% of infants. These cases are rare and do not have a distinct clinical phenotype. The numbers and individual cause - specific syndromes in this group are likely to increase as more pathogenic variants are found. Currently, none of the conventional antiseizure medications including glucocorticoids and pyridoxine stop the seizures. Nevertheless, treatment can be targeted at an underlying metabolic disorder, if present (e.g. aminoacidopathies or organic acidemias). Surgical removal of a focal lesion (including cortical dysplasias, hemimegaloencephaly and cortical tubers) if present, may be considered after the failure of two or more drug trials. These neonates may have coexisting movement disorders, cortical visual impairments, feeding difficulties or orthopedic problems due to abnormal muscle tone and contractures.

Prognosis and Complications

The prognosis for neonatal seizures varies according to the cause, age at onset, seizure duration and responsiveness to medication. Rapid recognition and treatment are considered the best ways to prevent adverse effects of the seizures and to improve long-term outcomes. Although self-limited epilepsy syndromes, described above, are characterized by frequent seizures, they remit spontaneously with a typically good prognosis. At the other extreme are the developmental and epileptic encephalopathies which are due to severe, diffuse brain injury often with a genetic cause and have a poor overall prognosis. Untreated seizures can cause hippocampal sclerosis and worsen the clinical outcome regardless of the cause. Despite this generally accepted tenet, the extent to which seizures can potentiate brain injury is unclear. Analyses of data from several case series have shown that status epilepticus or seizures lasting longer than 12 to 13 minutes per hour are associated with a poor outcome, which is independent of the cause.

Reference : N Engl J Med 2023; 388:1692-1700 (May 4, 2023)

Thalassemia

Thalassemias are a heterogeneous grouping of genetic disorders that result from a decreased synthesis of alpha or beta chains of hemoglobin (Hb). Hemoglobin serves as the oxygen-carrying component of the red blood cells. It consists of two proteins, an alpha and a beta. If the body does not manufacture enough of one or the other of these two proteins, the red blood cells do not form correctly and cannot carry sufficient oxygen; this causes anemia that begins in early childhood and lasts throughout life. Thalassemia is an inherited disease, meaning that at least one of the parents must be a carrier for the disease. It is caused by either a genetic mutation or a deletion of certain key gene fragments.

α - **thalassemia** is caused by α-globin gene deletion which results in reduced or absent production of α-globin chains.

β - **thalassemia** results from point mutations in the β-globin gene.

One mutated gene which is called thalassemia minor.

Two mutated genes which is called thalassemia major or Cooley anemia. Signs and symptoms will be moderate to severe.

Coinheritance of alpha thalassemia: β-thalassemia patients with coinheritance of α-thalassemia have a milder clinical course due to a less severe α-β chain imbalance.

Coexistence of sickle cell trait: The presence of sickle cell trait with β-thalassemia is a major hemoglobinopathy and results in manifestations of sickle cell disease.

Etiology

Thalassemia is autosomal recessive, which means both the parents must be affected with or carriers for the disease to transfer it to the next generation. It is caused by mutations or deletions of the Hb genes resulting in underproduction or absence of α or β chains. α-thalassemia is caused by deletions of α-globin genes and β thalassemias are caused by a point mutation in splice site and promoter regions of the β-globin gene on chromosome 11.

History and Physical

Thalassemia presentation varies widely depending on the type and severity. A complete history and physical examination can give several clues. The following findings can be noted :

- Fatigue due to anemia as the first presenting symptom
- Pallor due to anemia and jaundice due to hyperbilirubinemia
- Extremities examination can show ulcerations
- Extramedullary expansion of hematopoiesis results in deformed facial and other skeletal bones and an appearance known as chipmunk face.
- Arrhythmias
- Hepatosplenomegaly
- Chronic liver failure or cirrhosis
- Diabetes mellitus
- Hypothyroidism and hypoparathyroidism

Evaluation

Complete blood count (CBC): CBC is often the first investigation in a suspected case of thalassemia. A CBC showing low hemoglobin and low MCV is the first indication of thalassemia after ruling out iron deficiency anemia. The calculation of the Mentzer index (mean corpuscular volume divided by red cell count) is useful. A Mentzer lower than 13 suggests that the patient has thalassemia and an index of more than 13 suggests that the patient has anemia due to iron deficiency.

Peripheral blood smear: Thalassemia can present with the following findings on the peripheral blood smear: Microcytic cells (low MCV), Hypochromic cells, Variation in size and shape (anisocytosis and poikilocytosis), Increased percentage of reticulocytes, Target cells and Heinz bodies.

Iron studies: Serum iron, Ferritin, Unsaturated iron-binding capacity (UIBC), Total iron-binding capacity (TIBC) and Percent saturation of transferrin.

Erythrocyte porphyrin levels

Hemoglobin electrophoresis

DNA analysis: These tests serve to help confirm mutations in the α and β globin-producing genes.

Genetic testing of amniotic fluid: It is useful where a fetus has an increased risk for thalassemia.

Multisystem evaluation: Biliary tract and gall bladder imaging, Abdominal ultrasonography, Cardiac MRI, Serum hormone measurements .

Treatment

Thalassemia treatment depends on the type and severity of the disease.

Mild thalassemia (Hb: 6 to 10 g/dl):

Signs and symptoms are generally mild with thalassemia minor and little if any, treatment is needed. Occasionally, patients may need a blood transfusion, particularly after surgery following childbirth or to help manage thalassemia complications.

Moderate to severe thalassemia (Hb less than 5 to 6 g/dl):

- Frequent blood transfusions
- Chelation therapy
- Stem cell transplant
- Gene therapy
- Genome editing techniques
- Splenectomy
- Cholecystectomy
- Diet and exercise

Prognosis

Thalassemia minor is usually asymptomatic and has a good prognosis. It normally does not increase morbidity or mortality. Thalassemia major is a severe disease and the long-term prognosis depends on the treatment adherence to transfusion and iron chelation therapies.

Complications

Thalassemia major can produce the following complications:

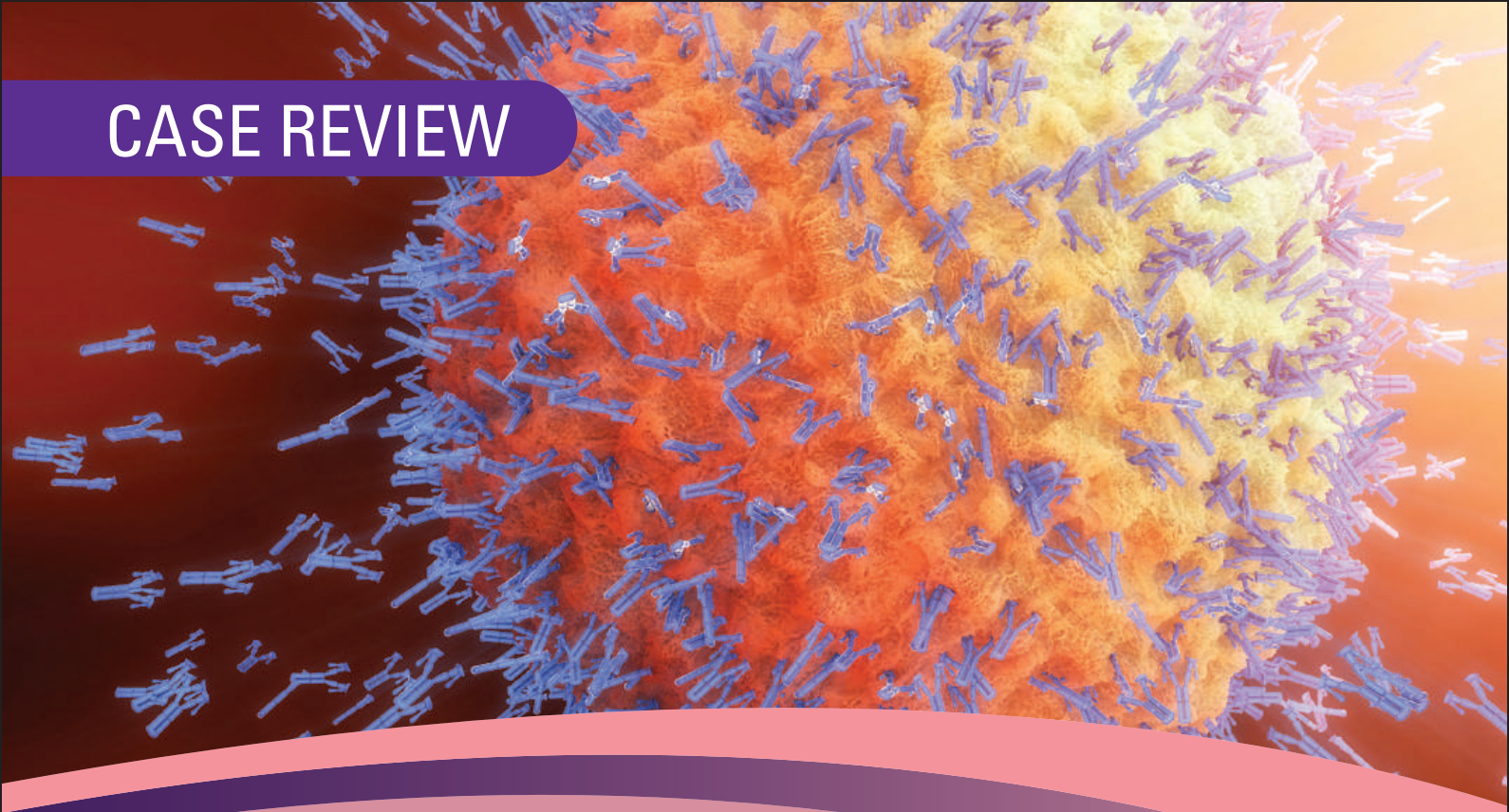
- Jaundice and gall stones due to hyperbilirubinemia.
- Cortical thinning and distortion of bones.
- Cardiac involvement
- Hepatosplenomegaly
- Excess iron can show findings of primary hemochromatosis such as endocrine abnormalities, joint problems, skin discoloration etc.
- Neurological complications
- Slow growth rate and delayed puberty.
- Increased risk of parvovirus B19 infection.

Patient Education

Patients should be educated to -

- Avoid excess iron
- Eat a healthy diet
- Avoid infections
- Education about the hereditary nature of the disease

Reference: https://www.ncbi.nlm.nih.gov/books/NBK545151/#article-30014.s6



Heparin-induced thrombocytopenia during IgA vasculitis: a case report

INTRODUCTION

Immunoglobulin A (IgA) vasculitis is characterized by small vessel vasculitis involving immune complexes and IgA deposition. Heparin-induced thrombocytopenia (HIT), a complication of heparin therapy, activates platelets, inducing thrombocytopenia and a prothrombotic state. The 4Ts score is required for clinical diagnosis; a definitive diagnosis can only be made if the serum anti-HIT antibodies are detected. Our patient exhibited acute kidney failure owing to IgA vasculitis and HIT on initiating dialysis.

CASE PRESENTATION

An 87- year - old man was being treated for chronic kidney disease at a local clinic. He was referred to hospital because of general fatigue and leg edema. Physical examination at admission showed a clear consciousness, BP : 203/93 mmHg, Body temperature : 36.0°C and SpO2 : 98% on room air. Mild pitting edema was observed on both lower legs. The serum creatinine level : 44 mg/dl (normally around 1.1 mg/dl) on the day of hospitalization ; blood and urine test results at admission are shown in Table 1. Arthritis of the right hand was observed on admission. Palpable purpura on both upper and lower limbs was observed from Day 4 and spontaneous pain and tenderness of the entire abdomen was observed from Day 5. Creatinine levels increased from 6.09 mg/dl on Day 8 to 10.1 mg/dl on Day 10 and blood clots were observed in the stool before dialysis. On Day 10, the patient presented with purpura (Fig.1), arthritis and renal involvement and was diagnosed with IgA vasculitis.

Blood and urine tests on Day 1

Test parameters	Laboratory test value	Normal range
White blood cells	14 000/µl	3000 - 8300/µl
Neutrophils	84%	41 - 74%
Lymphocytes	5%	18 - 48%
Eosinophils	4%	0 - 5%
Hemoglobin	11.7 g/dl	13.5 - 17.5 g/dl
Mean corpuscular volume	77.3/fl	85 - 102/fl
Platelets	246 x 10^3/µl	130 - 330 x 10^3/µl

Test parameters	Laboratory test value	Normal range
Prothrombin time/ International normalized ratio	1.08	0.85 -1.15
Activated partial		
thromboplastin time	25.7 s	24.3 - 36.0 s
Fibrinogen	232 mg/dl	150 - 400 mg/dl
Fibrin degradation product	15.1 µg/ml	0 - 9.9 µg/ml
D-dimer	6.7 µg/ml	0 - 0.99 µg/ml
Total protein	5.2 g/dl	6 - 8.4 g/dl
Albumin	2.4 g/dl	3.1 - 5.5 g/dl
Lactate dehydrogenase	251 U/l	106 - 211 U/l
Creatine phosphokinase	74 U/l	30 - 180 U/l
Blood nitrogen urea	50.5 mg/dl	6.2 - 19.4 mg/dl
Creatinine	4.45 mg/dl	0.8 - 1.2 mg/dl
Estimated glomerular filtration rate	10.5 ml/min/1.73 m^2	
Sodium	123 mEq/l	136 - 148 mEq/l
Potassium	3.0 mEq/l	3.6 - 5 mEq/l
C - reactive protein	1.03 mg/dl	0 - 0.6 mg/d
Urine specific gravity	1.007	1.002 -1.03
Urinary protein	3+	
Occult blood in urine	3+	
Leukocytes in urine	Negative	
Bacteria	Negative	
Granular casts	30 - 49/full field	
Hyaline casts	50 - 99/full field	
Waxy casts	+/full field	
Urinary protein	14.57 g/g Cr	

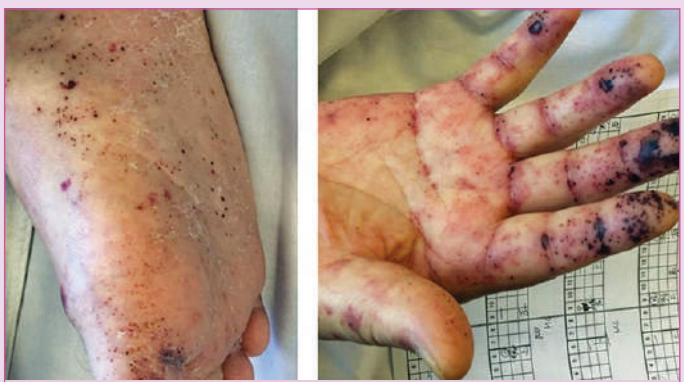


Figure 1 : Skin findings on Day 10; worsening of purpura was observed on both the hands, lower legs, soles and dorsum pedis.

Results of blood tests performed for differential diagnosis are shown in Table 2.

Table 2 : Additional blood tests on Day 4

Test parameters	Laboratory test value	Normal range
Anti-streptolysin O	5 IU/ml	0 - 240/IU/ml
Anti-streptokinase antibody	1: 5	1: 0 - 99 999
Syphilis rapid plasma reagin	Negative	
Quantitative treponema pallidum hemagglutination	80%	0 - 79.9%
Antinuclear antibodies	1: 40	1: 0 - 39.9
SS-A antibodies	1.0 U/ml	0.0 - 9.99 U/ml
SS-B antibodies	1.0 U/ml	0.0 - 9.99 U/ml
Proteinase 3 antineutrophil cytoplasmic antibodies	1.0 U/ml	0 - 3.49 U/ml
Myeloperoxidase - ANCA	1.0 U/ml	0 - 3.49 U/ml
Anti-glomerular basement membrane antibodies	2.0 U/ml	0 - 2.99 U/ml
IgA antibodies	223 mg/dl	80 - 450 mg/dl
IgG antibodies	446 mg/dl	800 - 1800 mg/dl
IgM antibodies	98 mg/dl	60 - 280 mg/dl
Hepatitis B surface antigens	0.3 COI	0 - 0.9 COI
HBS antibodies	0.2 mIU/ml	0 - 9.9 mIU/ml
Hepatitis C virus antibodies	0.1 COI	0 - 0.9 COI
Soluble IL2 receptor antibodies	1950 U/ml	145 - 519 U/m
Coagulation factor XIII activity	34%	70 - 140%

Ig (Immunoglobulin) ; HBS (Hepatitis B surface)

Regarding the treatment of IgA vasculitis, the patient and his family were advised on the need for treatment with steroids. Hemodialysis (HD) was administered thrice weekly since Day 11 (Fig. 2). Until Day 13, unfractionated heparin was administered both as an anticoagulant in the circuit and for flushing the route. From Day 14, the anticoagulant in the circuit was switched to low-molecular-weight heparin (LMW) and unfractionated heparin was used to flush the route. On Day 21, the pressure in the dialysis circuit increased during hemodialysis, causing interruption. The patient was switched to continuous hemodiafiltration (CHDF) on the same day owing to worsening symptoms of congestion caused by inadequate hydration. On the same day, the patient and his family were advised on the need for treatment with steroids; after taking consent, betamethasone was started at a dose of 4

mg/day. The abdominal pain worsened; this was considered to be an abdominal symptom related to IgA vasculitis, and blood coagulation factor XIII was therefore administered. Furthermore, as the platelet count was 143 000/μl, the anticoagulant in the circuit was changed to nafamostat owing to gastrointestinal bleeding. On Day 24, the platelet count rapidly decreased to 18 000/μl. The 4Ts score was five points and heparin was discontinued. On Day 25, positive Barre signs in the right upper limb and difficulty in kneeling on the right lower limb were observed; thus, cerebral thrombotic symptoms of HIT were suspected and argatroban was initiated. This improved the dialysis circuit and stabilized the intracircuit pressure; therefore, the patient was switched back from CHDF to hemodialysis.

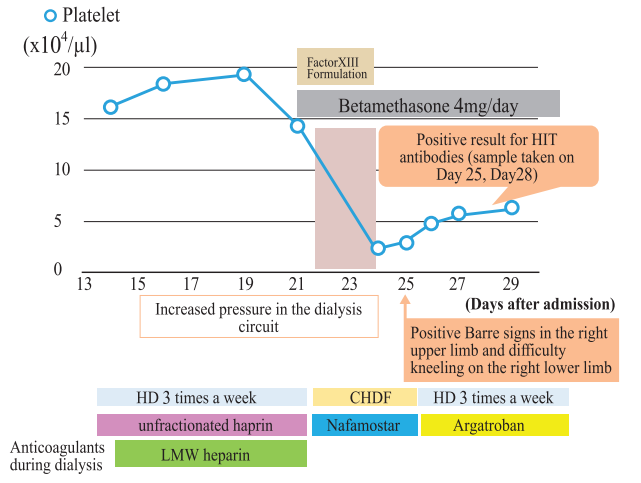


Figure 2 : Platelet count over time from Day 13 and treatment course

On Day 26, the paralytic symptoms disappeared; on Day 28, the patient tested positive for HIT antibodies (sample taken on Day 25), confirming the diagnosis of HIT, and on Day 34, the platelet count improved to 95000/μl. Betamethasone did not improve the renal function and resulted in steroid psychosis. Therefore, the patient's ability to provide informed consent for dialysis was lost, resulting in difficulties in performing the procedure. Eventually, on Day 59, he died of respiratory failure due to renal failure.

DISCUSSION

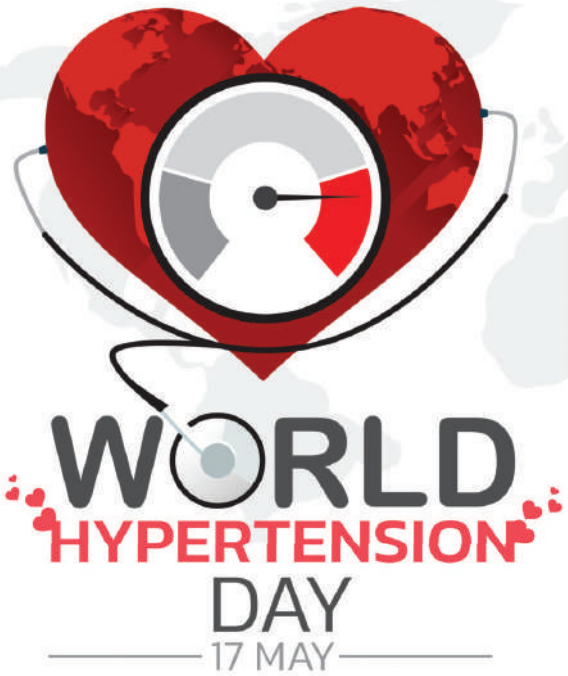
The patient was clinically diagnosed with IgA vasculitis. Skin and kidney biopsies were not performed because the patient did not provide consent. However, cholesterol crystal embolism was unlikely, as macrovascular surgery, catheterization and anticoagulant therapy had not been performed prior to the appearance of purpura. Regarding disseminated intravascular coagulation (DIC), the acute DIC score was three points (platelets only), which was negative; complement levels were not measured. Therefore, possible causes of palpable purpura were ruled out and the 2010 EULAR/PRINTO/PRES (purpura plus arthritis and renal involvement) and ACR classification criteria (palpable purpura and intestinal angina) were met; IgA vasculitis was diagnosed.

Abdominal symptoms may have been caused by thrombosis rather than by IgA vasculitis; however, abdominal imaging findings were only obtained using plain computed tomography (CT) throughout the course. It is unlikely that HIT was involved before the appearance of central nervous system (CNS) symptoms. Abdominal symptoms were present since admission, and they gradually worsened, suggesting that it was unlikely for the abdominal symptoms to be related to thrombosis.

Since the 4Ts score of the patient was five points based on thrombocytopenia over 50%, a significant decrease in platelet count 10 days after heparin administration and a lack of other causes of thrombocytopenia, HIT could not be excluded. HIT was diagnosed based on the 4Ts score and confirmed antibody positivity. HD circuit clots of unknown origin are the initial abnormality in HIT. In this patient, pressure in the dialysis circuit increased from Day 21, and platelet counts decreased from 193 000 to 143 000/μl (Fig. 2) ; this is abnormal in early stages of HIT. The onset of HIT is typically within 5 - 10 days. In the present case, the onset was on the 10th day after initiating heparin administration. The transiently occurring neurological symptoms (positive Barre signs in the right upper limb and difficulty kneeling on the right lower limb) may have been caused by HIT. Symptoms resolved 2 days after discontinuing heparin and 1 day after initiating argatroban. Intermittent use of heparin for dialysis may have led to mild symptoms. Cranial imaging was not feasible as he could not be transported.

Pathologically, IgA vasculitis is an immune-related leucocytoclastic vasculitis caused by IgA immune complexes with specific fibrin deposition in the vessel walls visible on immunofluorescence. It is unclear how IgA affects the pathogenesis of HIT. The association between IgA vasculitis and HIT is unknown and may have occurred incidentally while initiating hemodialysis. However, IgA vasculitis is presumably a systemic vasculitis, involving immune complexes and easily causes antibody production; this may have affected the HIT antibody production. Therefore, the occurrence of HIT should be considered in IgA vasculitis at the time of initiating dialysis.

Reference: Oxford Medical Case Reports, Volume 2021, Issue 3, March 2021



HEALTH DAY

World Hypertension Day

17 May, 2024

Measure Your Blood Pressure Accurately, Control It, Live Longer

World Hypertension Day is aimed at raising attention on the importance of hypertension control. This activity was started by the World Hypertension League (WHL) and was first held on May 14, 2005. Its purpose is to communicate to the public the importance of hypertension and its serious medical complications and to provide information on its prevention, detection, and management.

Raised blood pressure is the biggest single contributing risk factor to global health. More than one billion people around the world live with hypertension which is a major cause of cardiovascular disease and premature death worldwide. The burden of hypertension is felt disproportionately in low and middle income countries, where two thirds of cases are found, largely due to increased risk factors in those populations in recent decades. Around half of people living with hypertension are unaware of their condition, putting them at risk of avoidable medical complications and death.

WHO launched the Global Hearts Initiative to achieve the global target to reduce the prevalence of hypertension by 25% by 2025.

Reference: 1. https://www.paho.org/
2. www.whleague.org

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info MEDICUS
The essence of medical practice

INFO QUIZ CARD

(BMDC registered doctors only)

AMM/FM Territory Code……...

Name _____

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Address _____

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Read the questions, tick (√) the correct answers and hand over the Info Quiz Card attached to the Info Medicus to your nearest ACI representative by 30 June 2024.

1. **First line antiseizure medication is -**
   (a) Lidocaine (b) Phenytoin (c) Phenobarbital (d) Midazolam

2. **Which is not a key finding of thalassemia on the PBF?**
   (a) Ehrlich-Heinz bodies (b) Anisocytosis (c) Poikilocytosis (d) High MCV

3. **Normal range for IgA antibodies -**
   (a) 800-1800 mg/dl (b) 60-280 mg/dl
   (c) 40-240 mg/dl (d) 80-450 mg/dl

4. **4Ts scoring system excludes -**
   (a) Thrombocytosis (b) Thrombocytopenia
   (c) Thrombosis (d) Timing of thrombocytopenia

5. **Which of the following metabolic disorders is associated with neonatal seizures?**
   (a) Phenylketonuria (PKU) (b) Maple syrup urine disease (MSUD)
   (c) Wilson's disease (d) Fabry disease