Guideline for the investigation and treatment of Epilepsy in Infants less than Six Months

NHS Birmingham Women's and Children's NHS Foundation Trust

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1. Introduction and scope of guideline

- There are over 100 causes of epilepsy in the neonate/ infant.
- Many seizures may be provoked by an evident cause (hypoxic ischemic encephalopathy, infection, electrolyte disturbance, hypoglycaemia) the cause of which can be found on with basic laboratory investigations and MRI brain.
- ***This guideline is intended to outline a general approach to the investigation and treatment of children less than 6 months of age with unprovoked recurrent epileptic seizures.***
- The aim of the guideline is stream-line investigations and to identify common and treatable conditions with 'precision' therapy options being offered as appropriate
- Management of seizures in the context of Neonatal Hypoxic Ischemic Encephalopathy or other acute symptomatic aetiologies is not covered in this guideline.
- Investigation and management of Epileptic Spasms, which may present earlier than 6 months of age is covered in a separate guideline

2. Approach to investigation

Diagnosis of seizures based on clinical semiology +/- CFAM if available on NICU
Encourage parents to take videos of the events

First line immediate investigations in the Emergency Department

1. Blood gas/ glucose/ lactate/ renal profile/ magnesium/ bone profile/ CRP/ammonia
2. FBC/clotting
3. ECG
4. Consider lumbar puncture if infection suspected from the presentation MC+S, protein, paired glucose, paired lactate consider freezing and saving samples for CSF amino acids, and CSF neurotransmitters

First line urgent inpatient investigations

MRI brain (3T if possible) in all cases- day 3-7 of postnatal life if possible if HIE suspected. Consider MRS if available/ no structural abnormality found.

Ensure MRI reviewed by a Paediatric Radiologist at BCH.

Perform targeted investigations after discussion with Neurology if MRI shows an abnormality that points towards a specific diagnosis i.e. TORCH screen, targeted metabolic investigations, genetics for Tuberous Sclerosis

Second line investigations- where MRI non-diagnostic

1. Metabolic investigations- from blood- plasma amino acids, homocysteine, sulphocysteine, carnitine and free acylcarnitine profile, uric acid, biotinidase, transferrin glycoforms , very long chain fatty acids
2. Metabolic investigations from urine- urine organic acids, urine 5-AASA, urine creatinine and guadinoacetate, urine GAGs, urine oligosaccharides
3. Lumbar puncture- CSF neurotransmitters (if possible), CSF amino acids (specifically for CSF glycine and serine) if not already done
4. Genetics- microarray (liaise with genetics to process urgently) and save DNA

Third line investigations- if no cause apparent on second line investigations which are back

1. If baby admitted to NICU/PICU/ ward with uncontrollable seizures- to consider sending rapid whole exome sequencing to Exeter (2 week turn around)
2. If baby well enough for discharge home- to send off for the Great Ormond Street Early Infantile Epileptic Encephalopathy (EIEE) gene panel or 'Whole Genome Sequencing' when this becomes available in 2021
3. If ongoing seizures and a structural focal aetiology is still suspected then consider a repeat 3T MRI scan ideally before six months of age

Most common aetiologies of developmental epileptic encephalopathies

1. Structural- i.e. malformation of cortical developmental, perinatal stroke
2. Neurometabolic. Most common- sulfite oxidase deficiency, moldydenum co-factor deficiency, non-ketotic hyperglycinemia, pyridoxine dependent seizures
3. Neurogenetic- most common PRRT2, KCNQ2, SCN2A,SCNA1 related epilepsy

'Treatable' metabolic epilepsies not to miss

1. Glut- 1 deficiency. Initial investigation of choice- paired CSF/ plasma glucose. Treatment- ketogenic diet
2. Pyridoxine dependent seizures. Initial Investigation of choice- CSF PLP (need Neurotransmitter samples) or if CSF not possible urine 5-AASA but PNPO pathogenic variant will have a normal 5-AASA. Treatement- pyridoxine/ pyridoxal-5-phosphate + specialized diet
3. Folinic acid and pyridoxine responsive epilepsy. Investigation- CSF folate (need neurotransmitter samples). Treatment- folinic acid and pyridoxine supplementation
4. Biotinidase deficiency. Initial investigation- plasma biotinidase and urine organic acids. Treatment- biotin supplementation
5. Serine deficiency. Initial investigation- CSF amino acids. Treatment- specialized diet.
6. Phenylketonuria. Initial investigation- newborn serum screening card or plasma amino acids. Treatment- specialized diet.
7. Creatinine deficiency syndromes. Initial investigation- urine guanidinoacetate/ creatinine ratio. Treatment- specialized diet.

Organizing genetic/ metabolic investigations

- Liaise with the on-call Metabolic Laboratory Technician at BCH to ensure metabolic investigations are processed urgently. Most results will be available in less than 5 days in urgent cases.
- Neurotransmitters need to taken with special bottles in specific volumes and put straight into dry ice. These are sent to the Institute of Neurology (IoN) in London. Please liaise with the IoN directly to ensure samples are processed urgently.
- Note that CSF neurotransmitters, urine 5-AASA and creatinine/ guadinoacetate ratio are sent away so results may take several weeks. ***Consider sending off third line investigations before then***
- Liaise with the duty scientist at the West Midlands genetic laboratory to arrange urgent processing of a microarray
- Liaise with the on-call Consultant Geneticist if Whole Exome Sequencing is being considered

3. Approach to treatment

- Please liaise with the on-call Paediatric Neurology Consultant regarding choice of anti-epileptic medications in each individual case.
- Treatment choice should be tailored on the electroclinical diagnosis and the aetiology of epilepsy
- For infants less than 1 months consider levetiracetam (40mg/kg IV loading dose followed by 40mg/kg/day orally/ IV in two divided doses) or phenobarbitone (20mg/kg IV loading dose followed by 5mg/kg/day orally or IV in two divided doses) as a first line treatment.
- For children 1-6 months consider levetiracetam (40mg/kg/day in two divided doses) as a first line therapy
- If frequent ongoing short seizures, consider a loading dose of 20mg/kg of phenytoin (ideally IV but can be given orally). A significant response may indicate a genetic epilepsy affecting Sodium/ Potassium channel.
- Ensure that 'treatable metabolic' epilepsies have been excluded as specific treatments are required.
- Avoid Sodium Valproate particularly if a mitochondrial disorder is being considered.
- Many children with epilepsy presenting at this age will have drug resistant seizures so non-drug options such as Epilepsy Surgery and the Ketogenic Diet should be considered early where appropriate
- Many children with early onset epilepsies will require inpatient transfer to BCH for ongoing investigation/ seizure management so please liaise closely with the on-call Paediatric Neurology Team.

4. Framework to treatment based on the electroclinical diagnosis and/or aetiology

Electroclinical diagnosis suggestive of Ohtahara Syndrome or Early Myoclonic Encephalopathy- tonic seizures (+/- myoclonic seizures) with a burst suppression pattern on EEG	Seizures often extremely drug refractory Aim to minimize distressing and prolonged seizures only Supratherapeutic levels (10-15mg/L) of phenobarbitone in the palliative management of seizures can be considered Consider treatment with steroids- ACTH or prednisolone Consider ketogenic diet after 1 month of life.
Electroclinical diagnosis suggestive of genetic channelopathy (i.e. SCN2A, KCNT1, KCNQ2)- multifocal independent seizures or Electroclinical Diagnosis of Epilepsy of Infancy with Focal Migratory Seizures (EIFMS)	If sustained response seen following phenytoin load then consider regular carbamazepine or phenytoin. Aim for phenytoin levels in a therapeutic range 6-15mg/L in neonates to 3 months and a range of 10-20mg/L in babies and children older than 3 months. Monitor for side effects of phenytoin. If using carbamazepine aim for a level >8mg/L (therapeutic range 4-12mg/L). If seizures not controlled, consider ketogenic diet after 1 month of life if frequent prolonged and distressing seizures
Electroclinical diagnosis suggestive of structural focal epilepsy with or without clear imaging abnormality- focal seizures with stereotyped lateralised semiology/ all seizures shown to be coming from same hemisphere on EEG	Urgent referral and discussion with the Children's Epilepsy Surgery Service for consideration of Epilepsy Surgery Consider early use of vigabatrin especially if a lesion is felt to be a tuber
Frequent hypermotor/ multifocal seizures with normal MRI interictal EEG may also be relatively normal- consider a vitamin responsive epilepsy	Liaise early with your pharmacy to source medications After discussion with Paediatric Neurology on a case by case basis consider 1. Test dose of IV 100mg pyridoxine (ideally with EEG/ CFM running). NB may precipitate apnoea so resuscitation equipment must be present 2. Trial of oral pyridoxine (30mg/kg/day in four divided doses) 3. Trial Pyridoxal-5-phosphate (50mg/kg/day in four divided doses) and 4. Trial of Folinic acid (5mg twice daily initially)
Prolonged seizures (particularly hemi-clonic) seizures in the context of a febrile illness or post immunizations	Consider SCN1A related genetic epilepsy (Dravet Syndrome or Generalized Epilepsy with Febrile Seizures +). Send off urgent GOSH EIEE gene panel. Avoid treatment with carbamazepine/ phenytoin.
Epileptic spasms	Please refer to the Epileptic Spasms Guideline

Consider a trial of pyridoxine/ pyridoxal-5-phosphate and/or folinic acid (particularly when epilepsy is of neonatal onset) in all epilepsies resistant to treatment with two drugs where no definite cause has been found. Biotinidase levels are usually available within 48 hours and thus treatment can be guided by this result.

5. Follow-up and summary

- ***Please discuss all new diagnoses with of an early onset epilepsy with the on-call Paediatric Neurology Consultant at BCH. This guideline is a framework for practice but all cases merit detailed discussion.***
- If a metabolic cause is strongly suspected please discuss with the on-call Inherited Metabolic Disease Consultant
- Ensure that all children with an early onset epilepsy/ developmental epileptic encephalopathy have follow-up with a Consultant Paediatric Neurologist and Local Acute Consultant Paediatrician with expertise in epilepsy
- Have a low threshold for referral to Child Development Centre/ Community Paediatrician for Neurodevelopmental and long-term follow-up
- Ensure that all families have access to an Epilepsy Specialist Nurse and Basic Life Support/ Rescue Medication training where appropriate prior to discharge

6. References

- Symonds, Joseph D., et al. "Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort." *Brain* 142.8 (2019): 2303-2318.
- Surtees, Robert, and Nicole Wolf. "Treatable neonatal epilepsy." *Archives of disease in childhood* 92.8 (2007): 659-661.