ONCOLOGICAL EMERGENCIES: MANAGEMENT OF ENCEPHALOPATHY IN HAEMATOLOGY AND ONCOLOGY PATIENTS

SETTING
Division of Women’s and Children’s Services

FOR STAFF
Medical staff looking after oncology/haematology and BMT patients, including out of hours cover

PATIENTS
Children and teenagers with cancer and having bone marrow transplant under the paediatric team

This document should act as a guideline on the initial management of a child or young person with an encephalopathic process within the haematology and oncology unit.

1.0 INTRODUCTION

Acute encephalopathy is a medical emergency

Children presenting or undergoing treatment for any malignant condition have additional risk factors for developing neurological complications. This may be as a result of a number of factors:

- **The underlying disease** e.g. primary central nervous system (CNS) lesion, leucostasis secondary to high count leukaemia or rarely a paraneoplastic phenomena that may precede diagnosis
- **The Treatment:** recognised chemotherapy-related complications such as ifosfamide encephalopathy, CNS infection secondary to immunosuppression or Methotrexate induced-leukoencephalopathy.
- **Complications of Treatment** e.g. renal failure secondary to Tumour Lysis Syndrome

Encephalopathy is a non-inflammatory diffuse brain dysfunction (eg metabolic and drug intoxication).

Encephalitis includes leptomeningeal inflammation with symptoms of both diffuse and focal pathology as well as meningitis.

Management of children with an encephalopathy of unknown origin requires early involvement of neurology, Paediatric Intensive Care Unit (PICU), Immunology and Infectious diseases/microbiology.
2.0 CAUSES

The following causes are applicable to all children but there are some causes that are particularly important in Haematology/Oncology patients.

**Metabolic**
- Hypoglycaemia
- Hyperglycaemia
- Hyponatremia
- Hyperm ntremia
- Uraemia
- Steroid withdrawal or Adrenal insufficiency following withdrawal of prolonged steroid use e.g. induction in Leukaemia therapy.

**Drug related**
- Steroid psychosis/depression
- Ifosfamide-related encephalopathy
- Melphalan, busulphan neurotoxicity
- Cyclosporin / tacrolimus neurotoxicity
- L-asparaginase induced thromboembolic disease
- Cytarabine encephalopathy
- Methotrexate leukoencephalopathy
- Cisplatin neurotoxicity
- Fludarabine
- 5 -Fluorouracil (5- FU)
- Gemcitabine
- Sedative analgesia and anti convulsants (carbamazepine, gabapentin, levetiracetam, lamotrigine, phenytoin, primidone, topiramate, valproic acid and vigabatrin)
- Opiates, benzodiazepines, phenothiazines, cannabinoids
- Newer agents including monoclonal antibody therapies

**Infection: Meningitis, encephalitis**
- Bacterial
- Viral
- Opportunistic, include fungal
- Neurosurgery-related (ventriculitis, shunt infection)

**Haemorrhage, thrombosis**
- Thrombocytopenia
- Diffuse intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Coagulation factor hypoproduction (malnutrition, malabsorption, L-asparaginase-related)
- Dehydration
- Sepsis
Tumour –related
- Primary CNS tumour
- Metastatic tumour
- Paraneoplastic
- Post-neurosurgery complication
  - Subdural / extradural collection, haematoma
  - Infection – ventriculitis, meningitis
  - Infarction, haemorrhage
  - Posterior fossa syndrome
  - Shunt dysfunction

Other
- Autoimmune vasculitis
- Seizures

Specific conditions:

Posterior reversible leuko-encephalopathy (PRES)
Well-described with typical clinical and radiological features:
- Encephalopathy
- Seizures
- Other neurological symptoms (often headache and visual symptoms)
- Characteristic lesions of posterior and white matter predominance.
- Hypertension
- Females > Male
- Can occur with many chemotherapeutic agents
  - docetaxel, carboplatin, vincristine, paclitaxel, irinotecan, bevacizumab
  - most chemotherapy used to treat acute lymphoblastic leukaemia.

Recovery is usually good and patients can be re challenged with the chemotherapy (not recommended for anti-VEGF therapies).

Management
- Supportive care
- Treat hypertension
- Withdraw implicated agent

Progressive multi-focal leuko-encephalopathy (PML)
Rare demyelinating disorder of the brain caused by a ubiquitous virus (JC virus) in patients with underlying immunosuppression.

BMT patients have the greatest risk.

Increased risk with: Rituximab, MMF, alemtuzumab, Fludarabine, Infliximab and other TNF-Alpha inhibitors
3.0 INVESTIGATIONS

Routine baseline investigations

FOR ALL NON-ROUTINE TESTS IDEALLY DISCUSS WITH APPROPRIATE DEPARTMENT BEFORE SENDING SAMPLES.

- Full Blood Count
- Clotting profile including fibrinogen
- Urea & Electrolytes, phosphate, Calcium
- Liver function tests
- CRP
- ESR
- Bacterial, viral and fungal cultures
- Viral/fungal serology
- Viral PCR
- Hepatitis serology
- Metabolic screen
- Autoimmune screen
- Trace elements
- Lumbar puncture
  - CSF opening pressure,
  - Cerebrospinal fluid (CSF) for protein, glucose, bacterial culture, virology, atypical infection (discuss if safe to do pre-imaging)
  - Discuss CSF PCR with virology. Remember simultaneous blood glucose

Lumbar puncture should be delayed if CT or MRI is indicative of raised intra-cranial pressure, if patient has convulsive status epilepticus, soon after a generalized seizure or if coagulopathy or thrombocytopenia

Baseline Imaging

- Magnetic Resonance Imaging (MRI) of head (if unable to get MRI obtain CT scan of head to exclude acute events and allow LP)
- Consider Magnetic Resonance Arteriogram (MRA)/ Magnetic Resonance Venography (MRV)

Other

- Electroencephalogram (EEG)
- Psychological assessment
- Document Methotrexate levels (if appropriate)
4.0 THERAPEUTIC OPTIONS

(For drug dosages see USEFUL DRUG DOSES)

There is often no obvious cause when a child becomes encephalopathic. A number of treatment options, therefore, must be considered simultaneously following the appropriate baseline investigations.

General Therapeutic Options:

- Control raised blood pressure
- Correct metabolic disturbances
- Correct clotting abnormalities
- Commence broad spectrum antibiotics
- Commence high dose antiviral therapy such as Aciclovir or Foscarnet if Cytomegalovirus (CMV) or herpes Simplex Virus (HSV) infections are a possibility
- Consider antifungal therapy
- Treatment of any seizures as per APLS Guidelines\(^1\)

Specific Therapeutic Options:

1. Ifosfamide Encephalopathy – Methylene Blue\(^{2,3}\) (Link Management of Ifosfamide Encephalopathy)
2. Methotrexate Encephalopathy- Usual management is supportive only. Theophylline\(^4\), dextromethorphan (“Robitussin”) \(^5\)
3. Vasculitis High dose Methylprednisolone
   Plasmapheresis\(^6\)

To arrange Plasmapheresis: Contact apheresis on 21092 (0117 9125724 for OOH medic on call).
5.0 USEFUL DRUG DOSES

Antibacterial/antiviral and antifungal agents—see MANAGEMENT OF INFECTION IN HAEMATOLOGY AND ONCOLOGY PATIENTS – COMMONLY USED DRUG DOSES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>FREQUENCY</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline</td>
<td>2.5mg/kg</td>
<td>IV</td>
<td>Stat over 1 hour</td>
<td>May be repeated depending on level.</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>30mg/kg</td>
<td>IV</td>
<td>Per day</td>
<td>Max 1 gram per day for 3 days followed by standard doses</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1mg/kg</td>
<td>IV</td>
<td>Stat</td>
<td>Max 4mg. May be repeated after 10 minutes</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.4mg/kg</td>
<td>IV</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td>Paraldehyde</td>
<td>0.8mls/kg</td>
<td>PR</td>
<td>Stat dose</td>
<td>Use premixed 50:50 solution</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>18mg/kg</td>
<td>IV</td>
<td>Stat over 20 minutes</td>
<td>ECG/Blood pressure monitoring is mandatory.</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>20mg/kg</td>
<td>IV</td>
<td>Over 10 minutes</td>
<td></td>
</tr>
<tr>
<td>Thiopentone</td>
<td>4mg/kg</td>
<td>IV</td>
<td>Stat</td>
<td></td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>50-100mg</td>
<td>IV</td>
<td>stat</td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan (“Robitussin”)</td>
<td>1-2mg/kg per dose</td>
<td>Oral</td>
<td>TDS/QDS</td>
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### Table A

#### REFERENCES

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#### RELATED DOCUMENTS AND PAGES

|   | MANAGEMENT OF INFECTION IN HAEMATOLOGY AND ONCOLOGY PATIENTS – COMMONLY USED DRUG DOSES |

#### AUTHORISING BODY

Paediatric Haematology, Oncology and BMT Quality Assurance Forum (Quaf)

#### SAFETY

Not applicable

#### QUERIES AND CONTACT

For clinical concerns please contact any of the following for advice:

- Paediatric Haematology Registrar: bleep 3495
- Paediatric Oncology registrar: Bleep 2950
- Ocean Unit (8am-6pm): 28145
- Starlight Ward: 28334
- Apollo 35 Ward: 28335
- Haematology or Oncology consultant (via switchboard)