:: Tuberous sclerosis

- This document is a translation of the French recommendations drafted by Dr. M. Chipaux, reviewed and published by Orphanet in 2007.
- Some of the procedures mentioned, particularly drug treatments, may not be validated in the country where you practice.

Synonyms:
Bourneville's disease

Definition:
Tuberous sclerosis is an autosomal dominant multisystemic genetic condition that can affect many organs: brain, skin, eye, heart, lungs and the kidney. It affects one in 7 to 8,000 people. Its main complications involve the nervous system (convulsions, intracranial hypertension), the kidneys (rupture of cysts and angiomyolipomas) and the lungs of adult females (rupture of bullae with lymphangioleiomyomatosis). It can be difficult to detect the clinical signs of these complications due to the intellectual deficiency or psychiatric problems that can be associated with the condition. A full clinical evaluation must be done if there is the slightest suspicion.

Further information:
See the Orphanet abstract

Pre-hospital emergency care recommendations
Call for a patient suffering from Bourneville's tuberous sclerosis

Synonyms

- Bourneville's disease

Aetiology

- benign multisystemic hamartomatous condition (brain, heart, lung, kidney, eye, skin) developing from certain embryonic cells

Special risks in an emergency

- convulsions that are often of a partial epilepsy type
- intracranial hypertension
- retroperitoneal haemorrhage (rupture of renal micro-aneurysms)
- cardiac rhythm problems (rare)
- pneumothorax (rare)

Frequently used long term treatments

- vigabatrin, carbamazepin, oxcarbazepin, stiripentol

Complications

- be suspicious of any developing epileptic crisis, problems of consciousness and cognitive functions that may be masked by intellectual deficiency (early intracranial hypertension)
- be suspicious of any lumbar pain (retroperitoneal haematoma)

Specific medical care prior to hospitalisation

- no specific treatment for convulsions
- consider a neurosurgical opinion for cases of intracranial hypertension
- anaesthetic precautions related to possible cardiac and renal insufficiencies

Recommendations for hospital emergency departments

Emergency issues

1. Neurological complications: Convulsions

60 - 80% of patients will develop epilepsy during childhood and before they are 1 year old in 2/3 of cases. It is an epilepsy with partial seizures that may sometimes be associated with generalised seizures. Epilepsy may start with infantile spasms during the first year of life. Partial seizures are directly related to the presence of intracerebral tumours which act as epileptogenic centres. If epilepsy starts early and is badly controlled, it can develop to a Lennox-Gastaut syndrome by the age of 4 - 5 years.

- **Emergency diagnostic measures**
  - The paraclinical evaluation is based on the clinical condition and the context of the seizures using the **standard protocols for managing convulsions**.

- **Emergency therapeutic measures**
  - Emergency care for seizures should be provided in accordance with the **standard protocols for managing convulsion seizures**. Their treatment **depends on the type of seizure and epileptic syndrome**.
  - Be aware of **drug interactions** when treating **with Stiripentol** (see the drug interactions section and the appendix)
  - **Rarely**, the seizures will develop to a **grand mal status** and the complications and care of this should be provided in accordance with the **standard protocols for managing grand mal** cases.
  - **In all cases**, it is important **not to interrupt the patient's normal treatment** in order to avoid causing convulsions due to rapid withdrawal of the treatment.

- Orientation
  - **For a short seizure with a triggering factor** (medicine withdrawal, fever, tiredness, toxic...): non-urgent neurologist or neuropediatrician consultation.
  - **For an unexplained seizure or when seizures are frequent,** the patient must be seen sooner by his/her neurologist or neuropediatrician with a view to modifying the treatment, if necessary.
  - **If a grand mal status occurs**, use the standard orientation protocol to refer the patient to normal hospitalisation or to the critical care service.

2. Neurological complications: Intracranial hypertension

Intracranial hypertension must be considered if, in addition to the standard clinical signs, there is an increase in the frequency of convulsions, the type of seizure is different, there is a cognitive deterioration or an altered state of consciousness. Intellectual deficiency may make the diagnosis difficult and mask the usual clinical signs. The intracranial hypertension is linked to the presence of sub-ependymal nodules and giant cell astrocytomes where the increased size near Monroe's bursa can hinder the flow of cerebro-spinal fluid. The sub-ependymal nodules are hyperdense, uniform, calcified lesions that do not take up contrast on a scan. The giant cell astrocytomes take up the gadolinium contrast for MRI. Whilst they are benign from an oncology perspective, they can cause hydrocephaly and intracranial hypertension. A surgical procedure or excision is then required, preferably as planned intervention.

- **Emergency measures**
  - A **neurological opinion** must be sought **urgently**.
  - The patient must be referred in accordance with the protocols for managing acute tumoral intracranial hypertension.

3. Renal complications

Renal involvement includes developing benign cysts, angiomyolipoma and malignant tumours. Renal cysts are found in about 20% of patients. The presence of numerous cysts can result in chronic renal insufficiency in 1-3% of cases. 60 to 80% of adult patients carry renal angiomyolipomas that are often bilateral. They are benign slow growing tumours. The blood vessels are often affected by micro-aneurysms that may rupture spontaneously. **These ruptures result in a retroperitoneal haemorrhage that may require an emergency nephrectomy and can even threaten the patient's life. Unusual lumbar pain should be a sign because it may be due to a pre-fissural syndrome caused by minor intratumorous haemorrhages.**

- **Emergency diagnostic measures**
  - **Scans and MRI** are currently the best examinations to identify dangerous angiomyolipomas.

- **Emergency therapeutic measures**
  - In the event of a rupture with retroperitoneal haemorrhage or pre-fissural syndrome, **a surgical opinion must be requested urgently.**
  - Preventing the rupture of a dangerous angiomyolipoma: there are two options - surgery or embolisation.
  - **Treating a rupture: emergency surgery** (most often a nephrectomy)
  - Avoid total nephrectomy as much as possible when there is a malignant tumour especially if the contra-lateral kidney has angiomyolipomas that could rupture.

4. Pulmonary complications

Pulmonary involvement typically involves a **lymphangioleiomyomatosis** (26 - 57% of cases according to studies), a progressive interstitial pulmonary condition that mainly affects young women. It is linked to the diffuse proliferation of abnormal smooth muscle cells leading to the development of multiple cystic lesions that have a characteristic tomodensitometric appearance. These lesions **can cause dyspnoea, chylothorax and pneumothorax when adult and can develop to chronic respiratory insufficiency and death. Lesions may be exacerbated during pregnancy.**

- **Emergency diagnostic and therapeutic measures**
  - **Pneumothorax**: according to standard protocols.
  - **Acute or chronic respiratory insufficiency**: according to standard protocols.

5. Cardiac complications

The presence of an **intracardiac rhabdomyoma can cause an obstructive syndrome, rhythm problems or even sudden death. These complications are very rare** compared to the frequency of these tumours during the first years of life. Most rhabdomyomas are asymptomatic and involute after a few years.

Drug interactions

- The absence of drug interaction with the patient's long-term treatment must be checked, especially when treating **with Stiripentol**. A list of this drug's interactions is included as an appendix.

Anaesthesia

- **Drug interactions** with long-term treatment are possible (appendix)
- **Take account of potential multiple organ involvement** (cardiac insufficiency and rhythm problems due to intracardiac rhabdomyoma, renal insufficiency due to multiple renal angiomyolipomas)

Additional therapeutic actions and hospitalisation

40% of patients affected by tuberous sclerosis are also mentally handicapped. Many complications occur during infancy. Both of these reasons mean that **it is best to have the family present during an emergency admission or for any hospitalisation.**
The normal treatment should not be interrupted, especially that used for the epilepsy.

Organ donation

- As the condition is multisystemic, **organ donation cannot normally be considered.** The transplant authority service must be contacted in all cases.

Documentary resources

- Curatolo P. Historical Background. In : Tuberous sclerosis complex : From basic science to clinical phenotypes. Ed. Mac Keith Press, London, 2003 ; 1-10.
- Bourneville DM (1880) Sclerose tubéreuse des circonvolutions cérébrales ; idiotie et épilepsie hémiplégique. Arch Neurol (Paris 1 : 81-91.
- Dulac O, Tuxhorn I. Infantile spasms and West syndrom. In : Epileptic in infancy, childhood and adolescence. Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P Ed. John Libbey Eurotext, Paris, 2005, 53-72.
- Nabbout RC, Chiron C, Mumford J, Dumas C, Dulac O. Vigabatrin in partial seizures in children. J. Child Neurol. 1997;12(3) 172-7.
- Chiron C, Dumas C, Jambaque I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. epilepsy Res. 1997;26(2):389-95.
- Koh S, Jayakar P, Dunoyer C, Whiting SE, Resnick TJ, Alvarez LA et al. Epilepsy surgery in children with tuberous sclerosis complex: presurgical evaluation and outcome. Epilepsia 2000;41(9):1206-13.
- Jambaque I, Chiron C, Dumas C, Mumford J, Dulac O. Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients. Epilepsy Res. 2000;38(2-3);151-60.
- Beaumanoir A, Bume W. Lennox Gastaut syndrom. In : Epileptic syndroms in infancy, childhood and adolescence. Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P Ed. John Libbey Eurotext, Paris, 2005, 125-148.
- Asano E, Chugani DC, Muzik O, Behen M, Janisse J, Rothermel R et al. autism in tuberous sclerosis complex is related to both cortical an subcortical dysfunction. Neurology 2001;57(7):1269-77.
- Baron Y, Barkovich AJ. MR imaging of tuberous sclerosis in neonates and younf infants. AJNR Am. J. Neuroradiol. 1999;20(5):907-16.
- Nabbout R, Santos M, Rolland Y, Delalande O, Dulac O, Chiron C. Early diagnosis of subependymal giant cell astrocytoma in children with tuberous sclerosis. J. Neurol. Neurosurg. Psychiatry 1999;66(3):370-5.
- Ewalt DH, Sheffield E, Sparagana SP, Delgado MR, Roach ES. Renal lesion growth in children with tuberous sclerosis complex. J Urol 1998; 160:141-145.
- Schillinger F, Montagnac R. Chronic renal failure and its treatment in tuberous sclerosis. Nephrol Dial Transplant 1996; 11:481-485.
- Harbayashi T, Shinohara N, Katano H, Nonomura K, Shimizu T, Koyanagi T. Management of renal angiomyolipomas associated with tuberous sclerosis complex. J Urol 2004; 171:102-105.
- Jozwiak S, Curatolo P. Hepatic, lung, splenic, and pancreatic involvement. In : Tuberous sclerosis complex : From basic science to clinical phenotypes. Ed. Mac Keith Press, London, 2003; 215-227.
- Jozwiak S. Ophtalmological manifestations. In : Tuberous sclerosis complex : From basic science to clinical phenotypes. Ed. Mac Keith Press, London, 2003 ; 170-179.
- Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006; 355: 1345-56.
- Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am. J. Hum. Genet. 2001;68(1):64-80.

- Yates J. Tuberous sclerosis. Eur J Hum Gen. 2006 ; 14, 1065-1073.
- Marcotte L, Crino PB. The neurobiology of the tuberous sclerosis complex. Neuromolecular Med. 2006;8(4):531-46

Appendix

1. Drug interactions with Stiripentol

The action of STIRIPENTOL on P450 cytochromes occurs mainly through CYP3 A3/4 but also involves CYP1A2 and CYP2D6. Interactions can be expected with drugs where the hepatic metabolism depends on these isoenzymes:

- THEOPHYLLIN
- oral anticoagulants
- ergot derivatives
- ERYTHROMYCIN
- anti-arrhythmics
- beta-blockers
- hypnotics
- antidepressives
- CYCLOSPORIN
- digitoxin
- testosterone
- LIDOCAIN (parenteral administration).

These interactions also involve other anti-epileptics, especially CARBAMAZEPIN, PHENYTOIN and CLOBAZAM. These are positive interactions that are used in combination therapy plans with STIRIPENTOL.

2. Products to be used with care

Care is recommended for all the following products (precautions of use). Their conjoint use requires heightened clinical monitoring when starting treatment with STIRIPENTOL and after stopping it. Usually any change of dose rates should be accompanied by an evaluation, prothrombin levels for oral anticoagulents, theophylinaemia with theophyllin and its salts, CARBAMAZEPINE plasma levels.

- Therapeutic classes
  - ANTIHISTAMINES
  - NON STEROIDAL ANTI-INFLAMMATORIES
  - BENZODIAZEPINS
  - BETA BLOCKERS
  - BIGUANIDES
  - HORMONAL CONTRACEPTIVES
  - HYPNOTICS
  - HYPOGLYCAEMOGENIC SULFAMIDES
  - DIVERS

- Products contraindicated with STIRIPENTOL:

ACTRON	GLIBENESE	PLANOR
ADEPAL	GLUCIDORAL	PONSTYL
ALEPSAL	GLUCINAN	PRAXINOR
ALGIMAX	GLUCOPHAGE	PRENOXAN
ALGISFIR	GYNOPHASE	PREVISCAN
ALGO-NEVRITON	GYNOVLANE	PROFENID
ALGOCRATIN	HALGON	PROTEISULFAN
ALKA-SELTZER	HAVLANE	RANGASIL
ANTIGRIPPINE MIDI	HEMAGENE	RANIPLEX
APAROXAL	HEMI-DAONIL	RHONAL
APESMONE	HEMINEURIN	RIVOTRIL
APRANAX	IMMENOCTAL	ROHYPNOL
APTINE	IMOVANE	RUMICINE
ARTEX	INDOCID	SALIPRAN
ARTHROCIN	SARGEPIRIN	INSOMNYL
ASCRIPTIN	ISOPTIN	SECTRAL
ASPEGIC	JUVEPIRIN	SELOXEN
ASPIRIN	KANEURON	SERESTA
ASSUR	KERLONE	SERIEL
AVLOCARDYL	LEXOMIL	SINTROM
AZANTAC	LIBRIUM	SONERYL
BEFRANE	LOPRESSOR	SONUCIANE
BETAPRESSIN	LOPRIL	SOPROL
BETARYL	LYSANXIA	SOTALEX
BI-PROFENID	MANDRAX	STAGID
BINOCTAL	MEDIATOR	STEDRIL
BRONCO-TULISAN	MEDROCYL	STILNOX
BRUFEH	MEGAZONE	SUPPONERYL
BUTAZOLIOINE	MEPRONIZIN	SUPPONIZIN
BUTOBARBITAL	MIGROVAL	SUPPONOCTAL
DIPHARMA	MIGLUCAN	SUPPOPTANOX
CATALGINE	MILLI-ANOCLAR	SURGAM
CEBUTID	MILLIGYNON	TAGAMET
CHRONO-INDOCID	MINAFENE	TEMESTA
CHYMALGYL	MINIDIAB	TENORMIN
CLARAGIN	MINIDRIL	TILCOTIL
CORGARD	MINIPHASE	TIMACOR
COUMADIN	MOGADON	TRANCOGESIC
DAONIL	MYSOLINE	TRANDATE
DEPAKIN	NAFROSYN	TRANXENE
DEPAMID	NEURINASE	TRANSICOR
DEPO-PROVERA	NEVRAL	TRENTOVLANE
DETENSIEL	NIFLURIL	TRIELLA
DETOXALGIN	NOCTADIOL	TRINORDIOL
DIABINESE	NOCTRAN	TROMEXANE

DIAFLEXOL	NOPRON	URBANYL
DIAMICRON	NORDAZ	VALIUM
DIAMOX	NORIEL	VALPROATE
DI-HYDAN	NORISTERAT	VARNOLIN
DINULCOR	NORMISON	VEGANIN
EUCALYPTOSPIRIN	NOVACTOL	VERATRAN
EUCALYPTIN ASP	NOVAZAM	VICTAN
EUGLUCAN	NUCTALON	VISKEN
EUMOTOL	PHENYLBUTAZONE	VODAL
GARASPIRIN	PHYSIOSTAT	VOLTARENE
GARDENAL	PINIZONE	XANAX
		ZARONTIN

These guidelines have been prepared in collaboration with Dr. M. Chipaux of the Centre de Référence des Epilepsies Rares, the Association Sclérose Tubéreuse de Bourneville, and Docteur Gilles SAMU-69 Lyon

These guidelines have been translated thanks to the financial support of Alexion. ALEXION

Latest update: 4th October 2007