Tuberous Sclerosis Complex

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Tuberous sclerosis complex (TSC)

- Objectives
  - Definition
  - Diagnostic criteria
  - Clinical manifestation
  - Surveillance and management
  - Diagnostic and follow-up Tool
  - Treatments

Definition

- Tuberous sclerosis complex (TSC) is a genetic disorder that causes non-malignant tumors to form in many different organs: brain, eyes, heart, kidney, skin and lungs.
- Inactivation of TSC1 or TSC2
  - TSC1 and TSC2 genes suppress tumor growth in the body by carefully regulating cell growth through inhibition of a protein called mTOR

Epidemiology

- Insidence 1:6000
- Affect 1-2 million worldwild
- 5000 person in Canada
- Under diagnosed

Manifestation and diagnostic criterias

MAJOR FEATURES		MINOR FEATURES	
1	Hypomelanotic macules (≥3, at least 5-mm diameter)	1	"Confetti" skin lesions
2	Angiofibromas (≥3) or fibrous cephalic plaque	2	Dental enamel pits (>3)
3	Ungual fibromas (≥2)	3	Intraoral fibromas (≥2)
4	Shagreen patch	4	Retinal achromatic patch
5	Multiple retinal hamartomas	5	Multiple renal cysts
6	Cortical dysplasias*	6	Nonrenal hamartomas
7	Subependymal nodules		
8	Subependymal giant cell astrocytoma		
9	Cardiac rhabdomyoma		
10	Lymphangioleiomyomatosis (LAM)†		
11	Angiomyolipomas (≥2)†		

Definite diagnosis: Two major features or one major feature with ≥2 minor features.

Possible diagnosis: Either one major feature or ≥2 minor features.

*Includes tubers and cerebral white matter radial migration lines.

†A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

Cond't

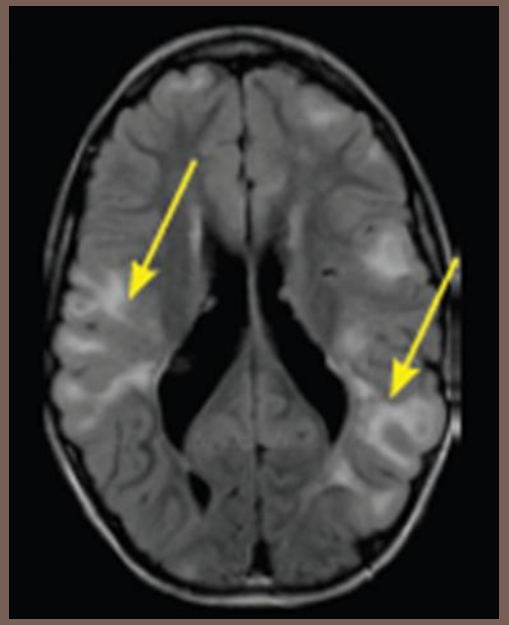
- GENE DIAGNOSTIC CRITERIA
  - The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a Definite Diagnosis of TSC

Brain Manifestation

- Epilepsy 90%
  - Infantile seizures 20-30%
- Brain tumors
  - Cortical tubers 90 %
  - SENs (Subependymal nodule) 95%
  - SEGAs (Subependymal giant cell astrocytomas) 6-19%

Cortical tubers 90 %

Collections of dysmorphic neurons, large astrocytes, and giant cells1,2
Epilepsy occurs in over 90% of patients and is associated with the presence of cortical tubers2

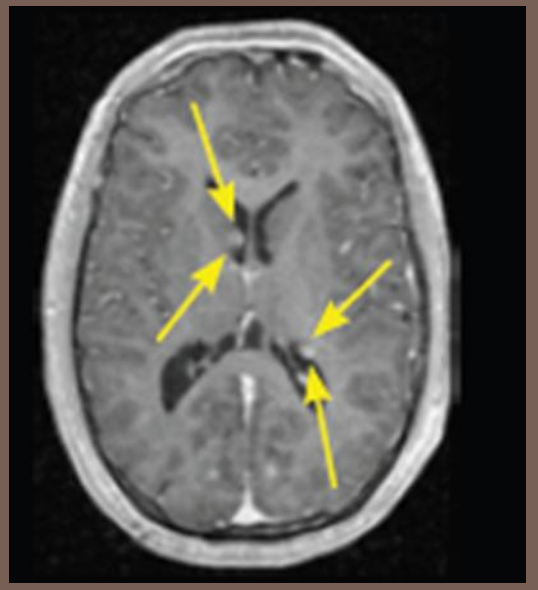


SENs (Sub ependymal nodule) 95%

Benign tumors, develop along ependymal lining of the lateral ventricles of the brain, proximal to the foramen of Monro1,3

SENs usually remain dormant and do not cause symptoms

Some SENs may increase in size to become SEGAs



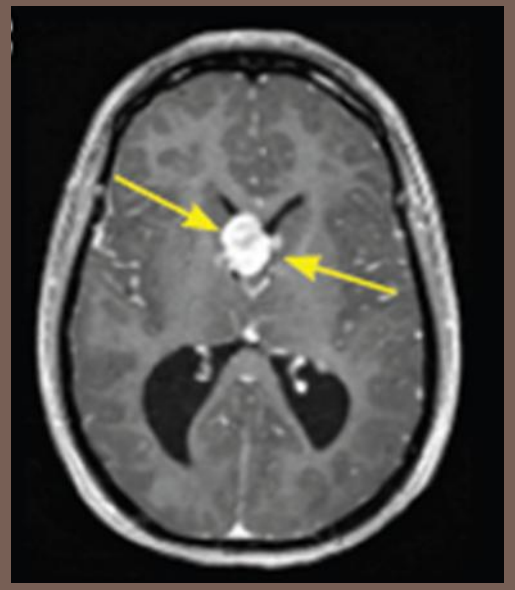
Numerous SENs distributed on the wall of the lateral ventricles

SEGAs (Subependymal giant cell astrocytomas) 6-19%

SEGAs are well circumscribed, slow-growing, low-grade tumors3

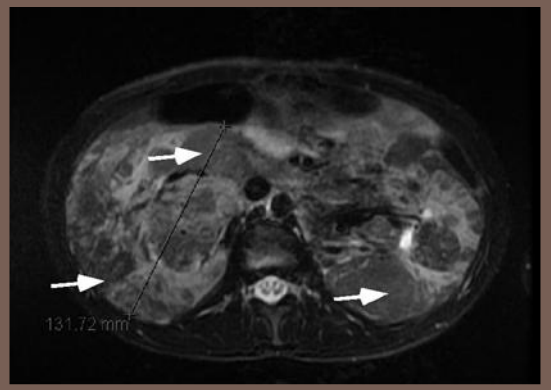
Can obstruct the CSF circulation, leading to hydrocephalus

Current intervention options:
Surgical resection, if feasible
Shunt implantation



A large SEGA along the midline of the brain near the foramen of Monro

Renal Manifestation



Angiomyolipoma

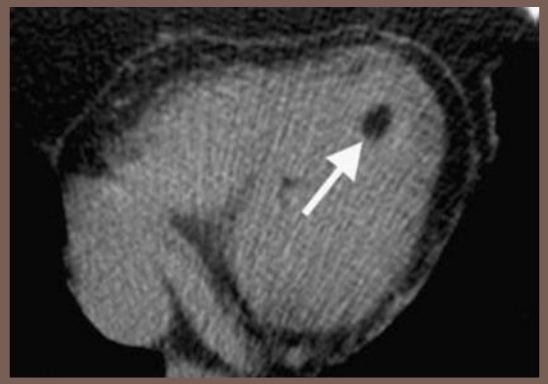
55 to 75%

Slow growing, bilateral kidney tumors
Complications due to mass effect: hemorrage or rupture of blood vessels feeding the lestion, destruction of adjacent renal tissue, risk of hypertension/renal failure

Cardio-pulmonary manifestations

- Cardiac rhabdomyomas 33-48%
- Lymphangioleiomyomatosis (LAM) 26-39%

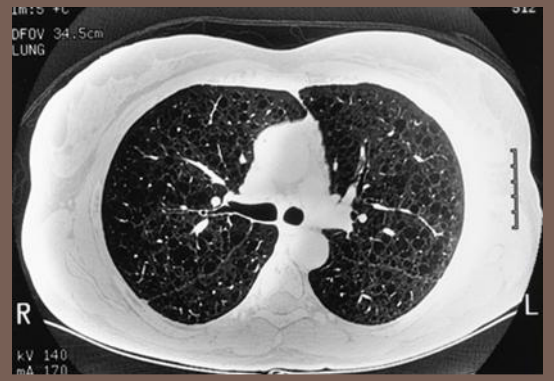
Cardiac rhabdomyomas



Cardiac rhabdomyoma

Present in 50-70% infants with TSC
Usually detected in utero or during the first year of life
Often regresses/disappears later in life
Although benign, position within critical areas in the heart may lead to lethal arrhythmias and heart failure

Lymphangioleiomyomatosis (LAM)

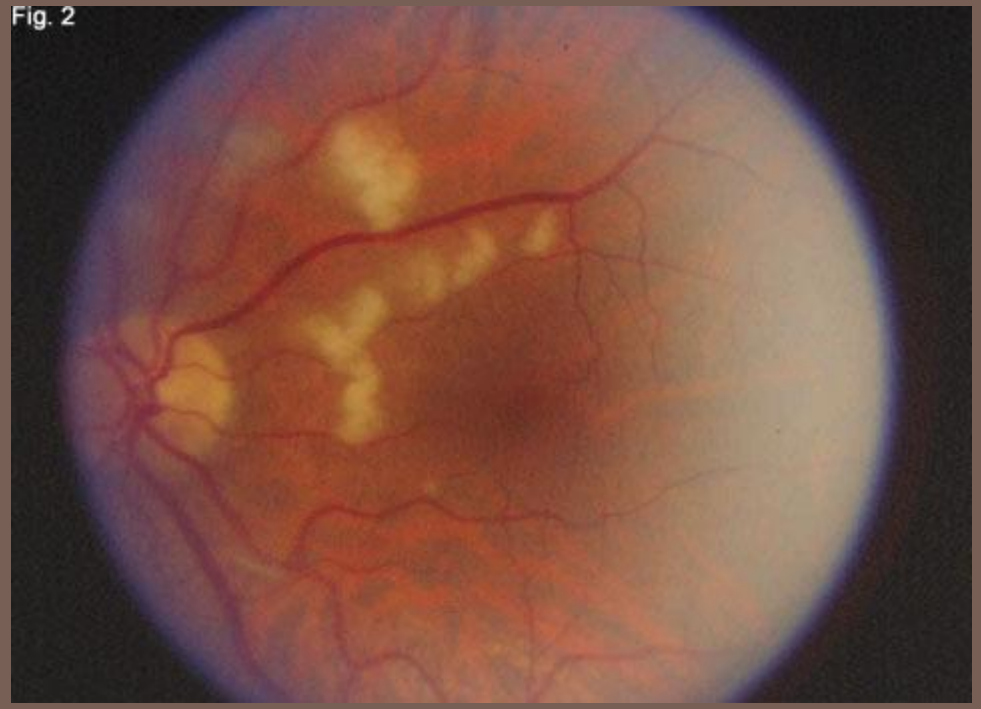


LAM

Progressive lung disease
Occurs in 30-40% of women with TSC
Infiltration of LAM smooth muscle cells and cystic destruction of the lung

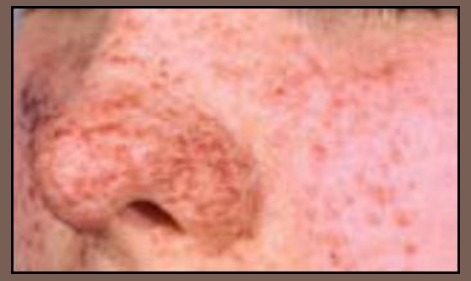
Ocular Manifestation

- Retinal lesions 40-50%

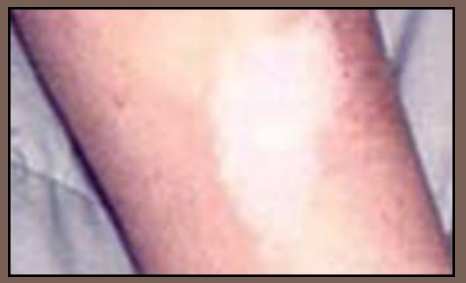


Skin Manifestation

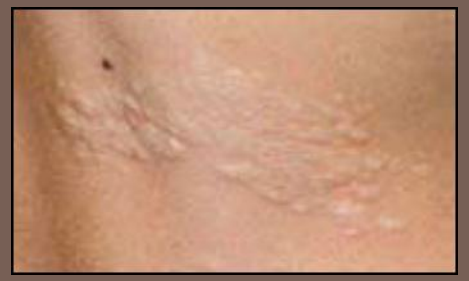
- Facial angiofibromas



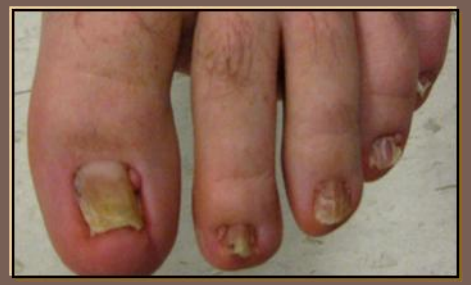
- Ash leaf spots



- Shagreen patches



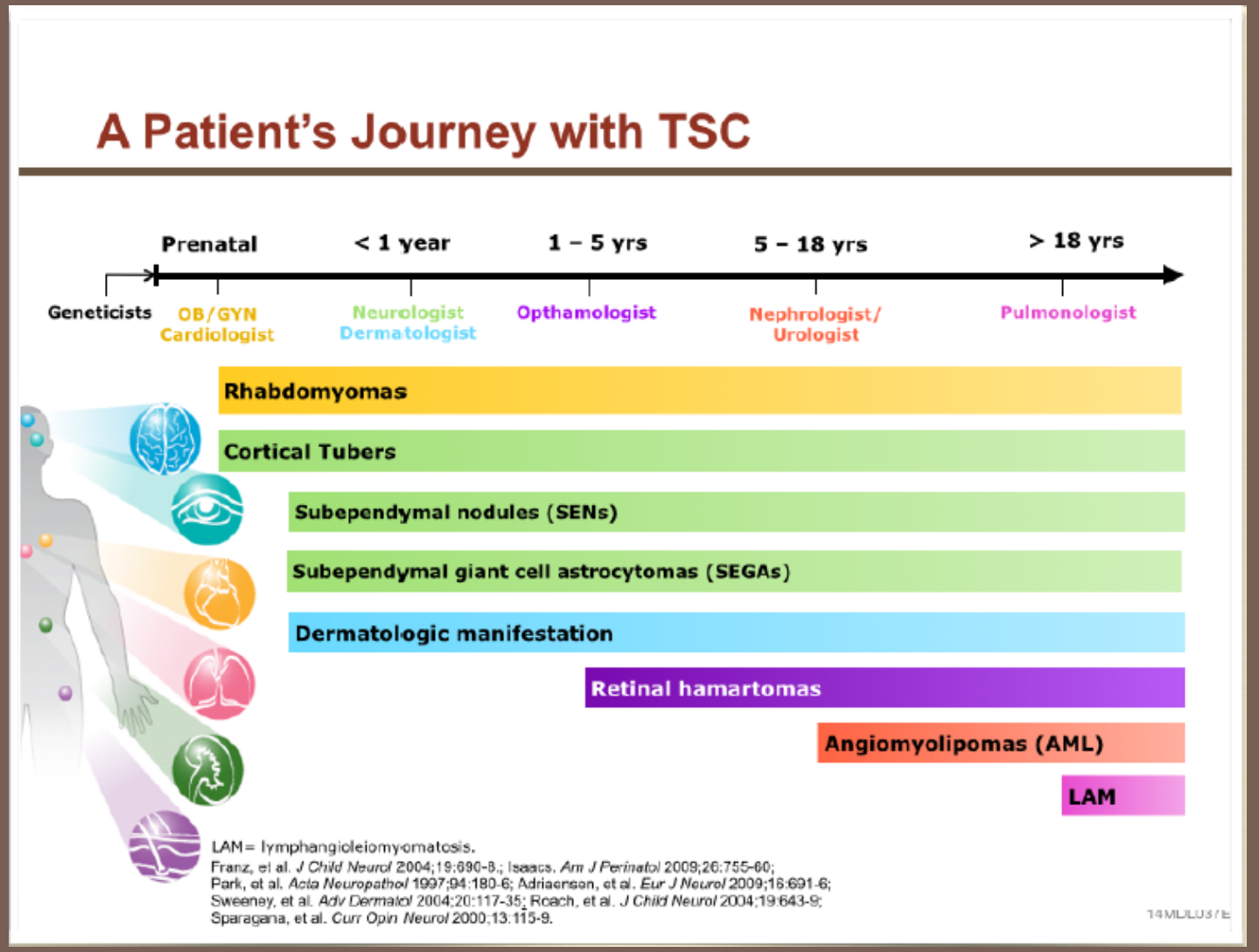
- Ungual fibromas



Developmental/ Behavioral Problems

- Cognitive dysfunction
- Autism spectrum disorder
- ADHD (attention deficit with hyperactivity disorder)
- Anxiety

Surveillance and recommandation



Cond't

- Pediatric specific surveillance
  - Fœtal EKG when cardiac rabdomyomas are detected on the echography
  - EKG 1-3 years
  - Teach parents to recognize infantil spasms

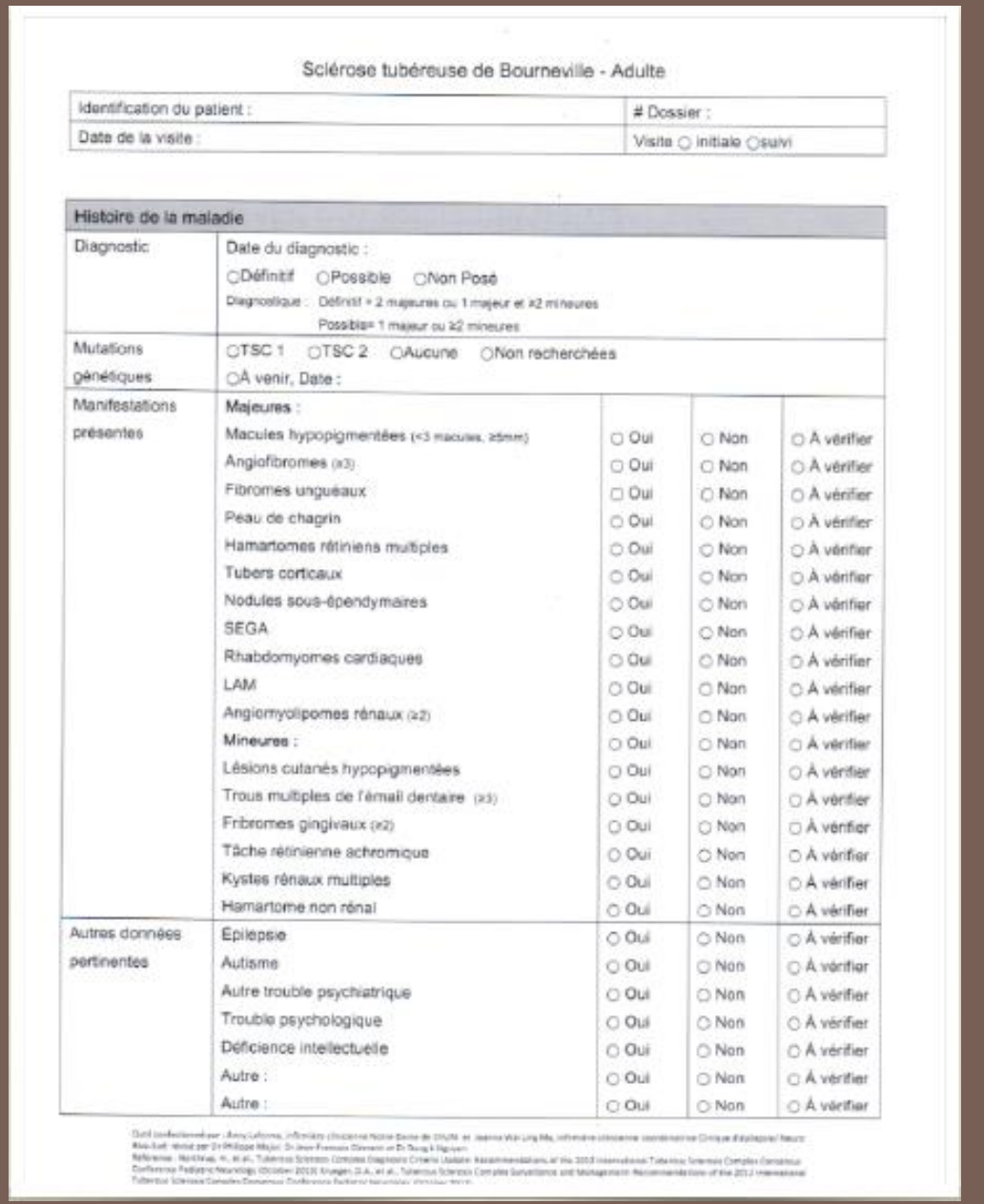
Cond't

- Specific to patient with SEGA:
  - MRI 1-3 years
  - MRI more frequently when growing SEGA of SEGA causing ventricular enlargement
  - Surveillance of Neurocognitive and comportemental disorders
  - EEG for epileptic patient and AEDs PRN

Cond't

- Specific to AML (renal)
  - Abdominal MRI 1-3 years
  - Annually renal function (including the glomerular function and Blood pressure)

Diagnostic and follow-up Tool

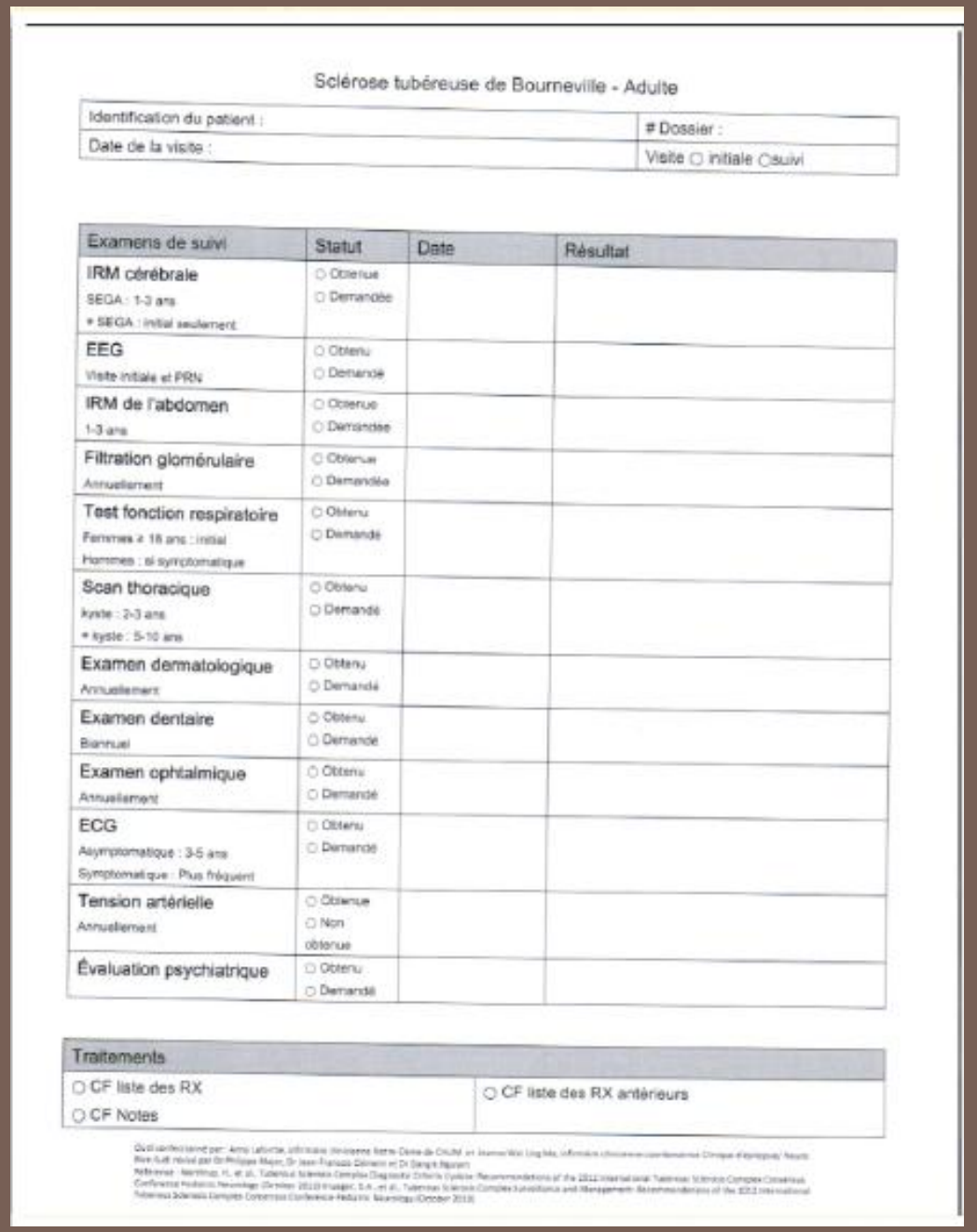


Sclérose tubéreuse de Bourneville - Adulte

Identification du patient :	# Dossier :
Date de la visite :	Visite ○ initiale ○ suivi

Histoire de la maladie				
Diagnostic	Date du diagnostic : ○ Définitif ○ Possible ○ Non Posé Diagnostique : Définit = 2 majeures ou 1 majeur et ≥2 mineures Possible= 1 majeur ou ≥2 mineures			
Mutations génétiques	○ TSC 1 ○ TSC 2 ○ Aucune ○ Non recherchées ○ À venir, Date :			
Manifestations présentes	**Majeures :**			
	Macules hypopigmentées (<3 macules, ≥5mm)	○ Oui	○ Non	○ À vérifier
	Angiofibromes (≥3)	○ Oui	○ Non	○ À vérifier
	Fibromes unguéaux	○ Oui	○ Non	○ À vérifier
	Peau de chagrin	○ Oui	○ Non	○ À vérifier
	Hamartomes rétiniens multiples	○ Oui	○ Non	○ À vérifier
	Tubers corticaux	○ Oui	○ Non	○ À vérifier
	Nodules sous-épendymaires	○ Oui	○ Non	○ À vérifier
	SEGA	○ Oui	○ Non	○ À vérifier
	Rhabdomyomes cardiaques	○ Oui	○ Non	○ À vérifier
	LAM	○ Oui	○ Non	○ À vérifier
	Angiomyolipomes rénaux (≥2)	○ Oui	○ Non	○ À vérifier
	Mineures :	○ Oui	○ Non	○ À vérifier
	Lésions cutanés hypopigmentées	○ Oui	○ Non	○ À vérifier
	Trous multiples de l'émail dentaire (≥3)	○ Oui	○ Non	○ À vérifier
	Fribromes gingivaux (≥2)	○ Oui	○ Non	○ À vérifier
	Tâche rétinienne achromique	○ Oui	○ Non	○ À vérifier
	Kystes rénaux multiples	○ Oui	○ Non	○ À vérifier
	Hamartome non rénal	○ Oui	○ Non	○ À vérifier
Autres données pertinentes	Epilepsie	○ Oui	○ Non	○ À vérifier
	Autisme	○ Oui	○ Non	○ À vérifier
	Autre trouble psychiatrique	○ Oui	○ Non	○ À vérifier
	Trouble psychologique	○ Oui	○ Non	○ À vérifier
	Déficience intellectuelle	○ Oui	○ Non	○ À vérifier
	Autre :	○ Oui	○ Non	○ À vérifier
	Autre :	○ Oui	○ Non	○ À vérifier

Cond't



Sclérose tubéreuse de Bourneville - Adulte

Identification du patient :	# Dossier :
Date de la visite :	Visite ○ initiale ○ suivi

Examens de suivi	Statut	Date	Résultat
IRM cérébrale SEGA : 1-3 ans * SEGA : initial seulement	○ Obtenue ○ Demandée		
EEG Visite initiale et PRN	○ Obtenu ○ Demandé		
IRM de l'abdomen 1-3 ans	○ Obtenue ○ Demandée		
Filtration glomérulaire Annuellement	○ Obtenue ○ Demandée		
Test fonction respiratoire Femmes ≥ 18 ans : initial Hommes : si symptomatique	○ Obtenu ○ Demandé		
Scan thoracique kyste : 2-3 ans + kyste : 5-10 ans	○ Obtenu ○ Demandé		
Examen dermatologique Annuellement	○ Obtenu ○ Demandé		
Examen dentaire Biannuel	○ Obtenu ○ Demandé		
Examen ophtalmique Annuellement	○ Obtenu ○ Demandé		
ECG Asymptomatique : 3-5 ans Symptomatique : Plus fréquent	○ Obtenu ○ Demandé		
Tension artérielle Annuellement	○ Obtenue ○ Non obtenue		
Évaluation psychiatrique	○ Obtenu ○ Demandé		

Traitements	
○ CF liste des RX ○ CF Notes	○ CF liste des RX antérieurs

Treatments

- Treatment aim to decrease symptoms (treat the symptoms)

Cond't

- For patient with SEGA
  - Symptomatic SEGA
    - Resective surgery
    - mTOR inhibitor
    - CSF (cerebral spinal fluid) Deviation
  - Surveillance of Neurocognitive and comportemental disorders
  - EEG and AEDs PRN

Cond't

- For patient with AML (renal)
  - If hemorrhage: embolisation and corticotherapy
    - Avoid nephrectomy
  - Growing AML > 3 cm
    - mTor inhibitor as first line therapy
    - Embolisation
    - Partiel resection acceptable as second line therapy

mTOR inhibitor

- Loss of TSC1/TSC2 in the mTOR pathway defines TSC
- The tuberous sclerosis complex (TSC1/TSC2) are tumor suppressor proteins
- Inactivation of TSC1 or TSC2 leads to increased mTOR activity

mTOR inhibitor regulates mTOR activity

References

- Northrup, H., et al., Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference Pediatric Neurology (October 2013)
- Krueger, D.A., et al., Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference Pediatric Neurology (October 2013)
- Roth, J., et al., Subependymal Giant Cell Astrocytoma: Diagnosis, Screening, and Treatment. Recommendations From the International Tuberous Sclerosis Complex Consensus Conference 2012 Pediatric Neurology (December 2013)
- TSC alliance website

Thanks!

- Question?