

Overgrowth associated syndrome  
**Sindrome di Sotos**

Epilessia e sindrome  
di Sotos



# Sindrome di Sotos

È una rara malattia genetica, anche detta gigantismo cerebrale, caratterizzata prevalentemente da

- supercrescita (**overgrowth**)
- dismorfismi del volto tipici
- ritardo dello sviluppo psicomotorio

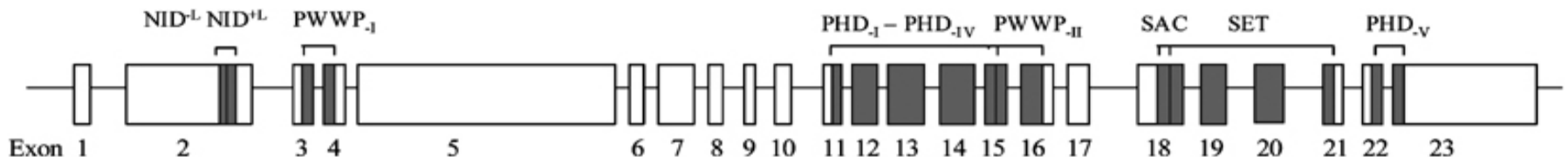
## Epidemiologia

L'esatta prevalenza è difficilmente valutabile a causa dell'ampia variabilità nell'espressione clinica è stimata approssimativamente 1/20000 nati.

# EZIOPATOGENESI

La sindrome è causata da mutazioni e delezioni del gene **NSD1** (Nuclear receptor **SET** domain containing protein-1) localizzato sul braccio lungo del cromosoma 5 che codifica per una metiltrasferasi istonica implicata nella regolazione della trascrizione.

## Schematic representation of NSD1



Negli ultimi anni l'analisi molecolare ha suggerito che anche altre mutazioni possano causare la sindrome in una percentuale più bassa di casi (cromosomi 10-14-X)

# Eziopatogenesi

Microdelezioni della regione cromosomica **5q35** → ritardo mentale più severo e iperaccrescimento meno marcato

Mutazioni puntiformi del gene **NSD1** → più frequente nelle popolazioni europee

La maggiorparte delle mutazioni avvengono **de novo**, ma sono descritti rari casi familiari con ereditarietà autosomica dominante

# Clinica

Le manifestazioni cliniche coinvolgono diversi organi e apparati

## Accrescimento staturo-ponderale

- superiore alla norma soprattutto nei primi anni di vita
- circonferenza cranica +1.85 DS
- peso +1 DS
- lunghezza +3.2 DS

## Alterazioni muscolo-scheletriche

- 84% età ossea
- 30% cifoscoliosi
- 20% iperlassità articolare
- piede piatto
- mani e piedi grandi



# Clinica

## Alterazioni craniofacciali

- macrodolicocefalia
- fronte ampia e prominente
- impianto alto dei capelli (radi)
- costrizione bitemporale
- ipertelorismo
- downslanting delle rime palpebrali
- narici anteverse
- palato ogivale
- prognatismo



# Clinica

## Alterazioni neuro-psicomotorie e comportamentali

- ipotonia alla nascita
- 30-50% convulsioni
- 45% EEG alterato
- 80% ritardo motorio e del linguaggio
- QI variabile
- memoria a breve termine
- calcolo matematico
- tratti autistici

## Difetti oculari

- Glaucoma
- Nistagmo
- Distrofia/atrofia retinica
- Megalocornea,
- ipoplasia dell'iride
- cataratta
- Strabismo e difetti rifrattivi nel 50% dei casi



# Clinica

## Difetti cerebrali

- ventricoli laterali
- ipoplasia del corpo calloso
- leucomalacia periventricolare

## Difetti cardiaci

DIA, DIV, PDA → incidenza molto diversa tra popolazioni caucasiche (8-20%) e giapponesi (35-50%)

## Apparato genitourinario

reflusso vescicoureterale

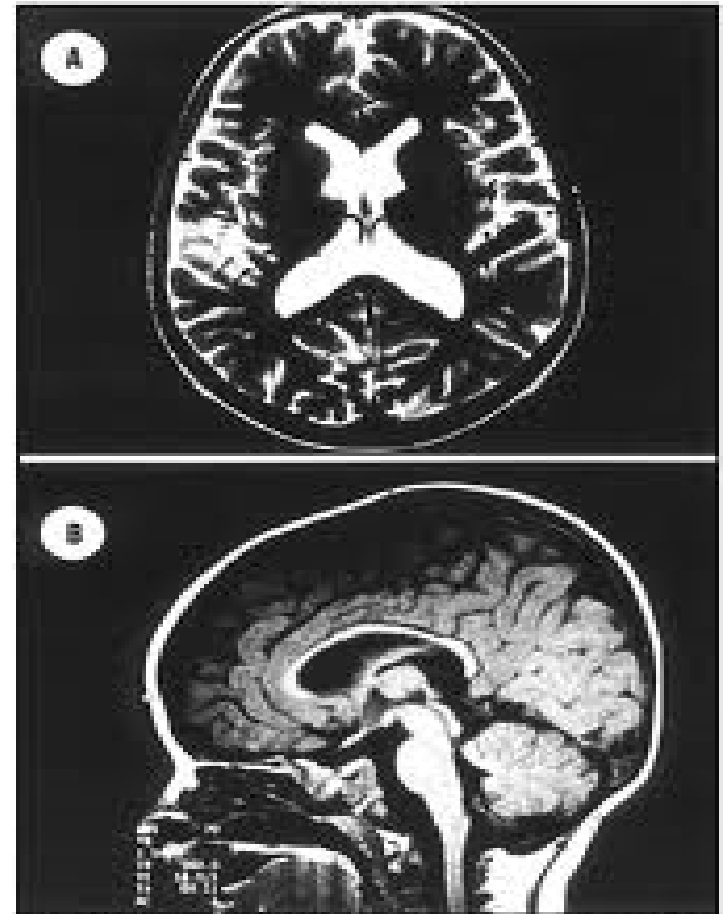


Fig 3. A) T1 weighted axial MRI image of patient 2 showing large global lateral ventricles. B) T1 weighted mid-sagittal MRI image shows hypoplasia of the corpus callosum and persistence of the cavum velum interpositum.

# Complicanze

## Neoplasie (2-3%)

tumore di Wilms, epatocarcinoma, parotidi, osteocondroma, neuroblastoma, emangiomi, LNH, LLA, microcitoma polmonare, testicolari, fibromi ovarici

## Infezioni

vie aeree superiori (72%)  
vie urinarie (20%)

## Endocrinopatie (14%)

iper/ipotiroidismo  
intolleranza al glucosio



# Diagnosi

- Non esistono criteri diagnostici ben definiti
- La clinica riveste un ruolo fondamentale e deve essere integrata da indagini radiologiche e riscontri anamnestici
- La *detection rate* dell'analisi genetica è <100% → la negatività dell'analisi molecolare non consente di escludere definitivamente la diagnosi
- Possibile diagnosi prenatale se a conoscenza della mutazione NSD1 in uno dei genitori



# Diagnosi

*Cardinal features - present in 90% of cases*

*Major features - present in 15% of cases*

Characteristic facial appearance

Advanced bone age

Learning disability

Cranial CT/MRI abnormalities

Childhood overgrowth

Poor feeding in infancy

Neonatal jaundice

Neonatal hypotonia

Seizures

Scoliosis

Cardiac anomalies

Renal anomalies

Maternal pre-eclampsia

Joint laxity/pes planus



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Short communication

## Long-term outcome of epilepsy in Kabuki syndrome

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### ABSTRACT

**Purposes and methods:** Kabuki syndrome (KS) is a rare dysmorphic disorder characterized by multiple congenital anomalies and mental retardation. Although epilepsy is one of the most common clinical complications associated with KS, few studies have evaluated its electroclinical aspects and long-term outcome. Therefore, we describe here a clinical series of 10 Caucasian KS patients who developed epilepsy in childhood. We followed all children for at least 5 years.

**Results:** All patients presented partial seizures and interictal EEGs revealed focal epileptic paroxysms with prevalent involvement of temporo-occipital areas. Seven children had no central nervous system abnormalities, but enlargement of lateral ventricles, corpus callosum hypoplasia, and adenohypophysis hypoplasia were revealed in three. Although antiepileptic drug (AED) treatment was effective in controlling seizures and normalizing EEG abnormalities in 8 patients, the other 2 cases were resistant to multiple AEDs. In one of these two patients, withdrawal of AED resulted in status epilepticus and death.

**Conclusions:** Partial seizures and temporo-occipital abnormalities on interictal EEG are common features of KS patients who suffer from epilepsy. Prognosis of this epilepsy is favourable in the majority of cases with complete disappearance of seizures and EEG abnormalities.

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### 1. Introduction

Kabuki syndrome (KS) is a rare dysmorphic syndrome of unknown cause, characterized by malformations affecting multiple organ systems and mental retardation.<sup>1,2</sup> KS was described for the first time in Japan in 1981 and it is now well recognized worldwide with an estimated incidence of 1 in 32,000 newborns.<sup>1–3</sup>

The most striking feature of an affected child is the facial appearance with eversion of low lateral eyelid, arched eyebrows, long palpebral fissures and prominent ears that is reminiscent of

subarachnoid cysts and malformations of cortical development can be expected in these patients.<sup>4–6</sup>

Although previous studies have reported epilepsy as one of the most common clinical complications associated with KS,<sup>1–3,7–10</sup> seizure semiology, electroencephalogram (EEG) findings and the natural course of epilepsy in these patients have not yet been fully described. Therefore, the purpose of this clinical series is to analyze the electroclinical aspects and the long-term outcome of 10 Caucasian KS patients with epilepsy.

### 2. Clinical series



## Seizures in fetal alcohol spectrum disorders: Evaluation of clinical, electroencephalographic, and neuroradiologic features in a pediatric case series

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### SUMMARY

Seizures are observed with a frequency of 3–21% in children with fetal alcohol spectrum disorders (FASD). However, clinical, neuroradiologic, and electroencephalography (EEG) features are poorly described. In this study, 13 patients with FASD and epilepsy or seizures were identified retrospectively from the databases of seven Italian pediatric neurology divisions. Eleven children were affected by epilepsy, and two had at least one documented seizure. Both generalized and focal seizures were observed. EEG showed diffuse or focal epileptic activity; two children developed electric status epilepticus during sleep (ESES). Structural brain anomalies, including polymicrogyria, nodular heterotopia, atrophy, and Arnold-Chiari type I malformation, were discovered in almost 50% of patients. Control of seizures was not difficult to obtain in 11 cases; one patient showed pharmacoresistant epilepsy. EEG and clinical follow-up are recommended in children with FASD and epilepsy, since severe conditions requiring aggressive treatment, such as in ESES, may develop. Neuroradiological evaluation is warranted because several types of brain anomalies could be associated with maternal alcohol consumption during pregnancy.

**KEY WORDS:** Fetal alcohol spectrum disorder, Fetal alcohol syndrome, Partial fetal alcohol syndrome, Alcohol-related neurodevelopmental disorders, Electroencephalography, Epilepsy.

## Epilepsy is a Possible Feature in Williams-Beuren Syndrome Patients Harboring Typical Deletions of the 7q11.23 Critical Region

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Seizures are rarely reported in Williams-Beuren syndrome (WBS)—a contiguous-gene-deletion disorder caused by a 7q11.23 heterozygous deletion of 1.5–1.8 Mb—and no previous study evaluated electro-clinical features of epilepsy in this syndrome. Furthermore, it has been hypothesized that atypical deletion (e.g., larger than 1.8 Mb) may be responsible for a more pronounced neurological phenotypes, especially including seizures. Our objectives are to describe the electro-clinical features in WBS and to correlate the epileptic phenotype with deletion of the 7q11.23 critical region. We evaluate the electro-clinical features in one case of distal 7q11.23 deletion syndrome and in eight epileptic WBS (eWBS) patients. Additionally, we compare the deletion size—and deleted genes—of four epileptic WBS (eWBS) with that of four non-epileptic WBS (neWBS) patients. Infantile spasms, focal (e.g., motor and dyscognitive with autonomic features) and generalized (e.g., tonic-clonic, tonic, clonic, myoclonic) seizures were encountered. Drug-resistance was observed in one patient. Neuroimaging discovered one case of focal cortical dysplasia, one case of fronto-temporal cortical atrophy and one case of periventricular

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### INTRODUCTION

Williams-Beuren syndrome (WBS; OMIM 194050) is a genetic disorder characterized by typical facial dysmorphisms, supraorbital

## Electroclinical Features and Long-Term Outcome of Cryptogenic Epilepsy in Children with Down Syndrome

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**Objective** To describe the electroclinical features and the long-term outcomes of epilepsy in a large cohort of males and females with Down syndrome who developed epilepsy in childhood.

**Study design** Subjects with Down syndrome and cryptogenic epilepsy with onset in childhood were identified retrospectively from the databases of 16 Italian epilepsy centers over a 40-year period. For each subject, age at onset of seizures, seizure semiology and frequency, electroencephalography characteristics, treatment with anti-epileptic drugs, and long-term clinical and electroencephalography outcomes were analyzed.

**Results** A total of 104 subjects (64 males [61.5%], 40 females [38.5%]) were identified. Seizure onset occurred within 1 year of birth in 54 subjects (51.9%), between 1 and 12 years in 42 subjects (40.4%), and after 12 years in 8 subjects (7.7%). Males had a younger age of seizure onset than females. Of the 104 subjects, 51 (49.0%) had infantile spasms (IS), 35 (33.7%) had partial seizures (PS), and 18 (17.3%) had generalized seizures (GS). Febrile seizures were recorded in 5 (4.8%) subjects. Intractable seizures were observed in 23 (22.1%) subjects, including 5 (9.8%) with IS, 8 (44.4%) with PS, and 10 (31.3%) with GS.

**Conclusion** Cryptogenic epilepsy in Down syndrome may develop during the first year of life in the form of IS or, successively, as PS or GS. Electroclinical features of IS resemble those of idiopathic West syndrome, with a favorable response to treatment with adrenocorticotrophic hormone seen. Patients experiencing PS and GS may be resistant to therapy with antiepileptic drugs. (*J Pediatr* 2013;163:1754-8).

With an estimated frequency of 1 in 730 live births,<sup>1</sup> Down syndrome is the most common genetic cause of intellectual disability. The reported prevalence of epilepsy in patients with Down syndrome ranges from 1% to 13%,<sup>2</sup> compared with 1.5%-5% in the general population.<sup>3</sup> The increased susceptibility to seizures in patients with Down syndrome may be related to the neurologic alterations, both morphological and physiological,<sup>4,5</sup> or the associated medical complications, such as cardiovascular abnormalities and recurrent infections, normally observed in this population.<sup>6</sup>

A triphasic distribution of epilepsy in Down syndrome comprising infancy epilepsy, early adulthood epilepsy, and a distinct epilepsy syndrome in patients aged >50-55 years has been identified.<sup>7,8</sup> In the youngest age group, infantile spasms (IS), with a late onset and a comparatively benign course,<sup>2,9</sup> is the most common form, whereas in the early adult group, partial seizures (PS) is the most common form. Generalized seizures (GS), including tonic-clonic seizures, seem to be distributed equally throughout the lifespan.<sup>3,10</sup>

To add to the knowledge base of the clinical course of epilepsy in Down syndrome, in the present study we examined the electroclinical features and long-term outcomes of epilepsy in a large cohort of males and females with Down syndrome who developed epilepsy during childhood.

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## Epilepsy in patients with Cornelia de Lange syndrome: A clinical series

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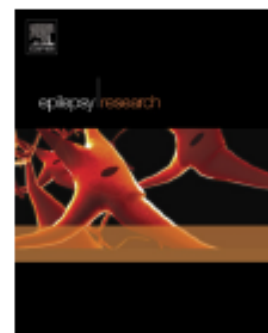
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# Epilepsy in Menkes disease: An electroclinical long-term study of 28 patients



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Mini review

# Ohtahara syndrome with emphasis on recent genetic discovery

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## Abstract

Ohtahara syndrome or Early Infantile Epileptic Encephalopathy (EIEE) with Suppression-Burst, is the most severe and the earliest developing age-related epileptic encephalopathy. Clinically, the syndrome is characterized by early onset tonic spasms associated with a severe and continuous pattern of burst activity. It is a debilitating and early progressive neurological disorder, resulting in intractable seizures and severe mental retardation. Specific mutations in at least four genes (whose protein products are essential in lower brain's neuronal and interneuronal functions, including mitochondrial respiratory chains have been identified in unrelated

## BRIEF COMMUNICATION

### Seizures and epilepsy in Sotos syndrome: Analysis of 19 Caucasian patients with long-term follow-up

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#### SUMMARY

Sotos syndrome (SS) is an overgrowth syndrome characterized by typical facial appearance, learning disability, and macrocephaly as cardinal diagnostic features. Febrile (FS) and afebrile seizures are reported in 9–50% of cases. There is no evidence that patients with SS and FS later develop epilepsy, and no studies have investigated the electroclinical features and the long-term outcome in epileptic SS patients. The authors report a series of 19 SS

patients with FS and/or epilepsy during childhood and a long-term follow-up. More than half of FS evolved to epilepsy. Temporal lobe seizures were recorded in 40% of patients with SS. Seizures were easy to control with common antiepileptic drugs in almost all patients. A careful neurologic evaluation is useful for SS patients, since seizures are an important finding among people with this overgrowth syndrome.

**KEY WORDS:** Sotos syndrome, Seizures, Epilepsy, Cerebral gigantism, Overgrowth syndrome.

- Most SS patients have non progressive neurologic dysfunction and brain anomalies.
- Neurologic disturbances associated with SS are hypotonia, feeding difficulties, clumsiness, poor coordination, delayed language and motor development, behavioral anomalies, and seizures.
- The degree of learning impairment is estimated to be extremely variable, although it is present in almost all patients(Tatton Brown et al.,2005).

- Several studies affirm that seizures may appear in about 15–50% of patients, and they are estimated to be febrile in half of cases (Tatton-Brown et al., 2005; Baujat & Cormier-Daire, 2007; Tatton-Brown & Rahman, 2007).
- A recent review of 21 SS adults described seizures as rare (9%) (Fickie et al., 2011).
- However, no data are available on whether patients with SS and febrile seizures (FS) later develop epilepsy, and no studies have investigated the electroclinical features and the long-term outcomes of epilepsy in these patients.

- The aim of this study is to analyze the neurologic profile of 19 Caucasian patients with SS, with particular regard to epileptic phenotype and outcome.

# Methods

- To be eligible for this study, patients had to have been clinically diagnosed with typical SS (e.g., presence of all the cardinal features in the same patient) (Tatton-Brown & Rahman, 2007) and had to present with at least one FS or afebrile seizure (AF).

# Methods

- All the patients had to have undergone full neurologic examination, brain magnetic resonance imaging (MRI), EEG recording, and long-term clinical and EEG follow-up.
- Age at onset of seizures, seizure semiology, EEG characteristics, brain MRI findings, and therapy with antiepileptic drugs (AEDs) were analyzed for each case.

- Genetic analysis of exons 2–23 of the NSD1 gene was performed in the reported patients by means of denaturing high performance liquid chromatography (HPLC; Transgenomics, Omaha, NE, U.S.A.), and direct sequencing of the chromatographic variant on 3130xl sequencer (Applied Biosystems, Foster City, CA, U.S.A.).
- Seizures were classified according to criteria of the International League Against Epilepsy (ILAE) (Engel, 2001).
- Written informed consent was obtained from parents or guardians of all recruited people.

# Results

- Data from 19 Caucasian patients (15 male, four female) were collected from a cohort of patients referred to eight Italian Pediatric Neurology Divisions.
- The mean age at time of first evaluation was of 5 years 2 months (range 4 months–15 years), and the mean age at time of last follow-up was of 11 years 2 months (range 6–20 years).
- Minimum follow-up period was of 5 years (range 5–19 years). Febrile and afebrile seizures were recorded in 11 and 15 patients, respectively; seven children with FS developed generalized and/or focal AF.
- Clinical, neurologic, neuroradiologic, and genetic features of the 19 patients are summarized in Table 1.

**Table 1. Summary of the 19 reported patients with SS**

<i>Cardinal Sotos syndrome features and genetic analysis</i>			
Facial gestalt		NSD1 analysis	
Yes	19 (100%)	NSD1-mutated SS patients	14 (74%)
No	–	Non-NSD1-mutated SS patients	5 (26%)
Overgrowth with macrocephaly		Type of NSD1 point mutation	
Yes	19 (100%)	Missense	10 (71%)
No	–	Frameshift	4 (29%)
Learning disability			
Yes	19 (100%)		
No	–		
Seizures' features			
Seizures [Mean age of onset]			
Only febrile		4 (21%) [1 year 6 months]	
Only afebrile		8 (42%) [6 years 2 months]	
Febrile → Afebrile		7 (37%) [1 year 5 months → 4 years 9 months]	
Seizure type		EEG pattern	
Febrile (11 pts)		Febrile seizures	
Only simple	6 (55%)	Normal	4 (36%)
Only complex	1 (9%)	Diffuse anomalies (slow waves)	4 (36%)
Simple + complex	4 (36%)	Focal anomalies	
Afebrile (15 pts)		Centrottemporal area	3 (28%)
Only GTCS	5 (33%)	Afebrile seizures	
Only TLS	4 (27%)	Diffuse anomalies	1 (7%)
Only atonic seizures	2 (13%)	Focal anomalies	
Only frontal lobe epilepsy	1 (7%)	Frontotemporal area	5 (33%)
Only absence seizures	1 (7%)	Parietotemporoooccipital area	9 (60%)
Multiple seizures type <sup>a</sup>	2 (13%)	Response to AED therapy	
Patients requiring AED therapy		Febrile seizures	3 (100%)
Febrile seizures	4 (36%)	Afebrile seizures	
Afebrile seizures	15 (100%)	Monotherapy	12 (87%)
		Polytherapy	1 (6.5%)
		Drug-resistant epilepsy	1 (6.5%)
<i>Nonepileptic neurologic features and neuroimaging</i>			
Congenital hypotonia		Developmental delay	
Yes	17 (89%)	Yes	19 (100%)
No	2 (11%)	No	–
Other neurologic signs/symptoms		Neuroimaging	
Behavioral disturbances <sup>b</sup>	9 (47%)	LV enlargement	14 (74%)
Poor coordination	4 (21%)	SAS enlargement	7 (37%)
Ocular anomalies <sup>c</sup>	2 (10%)	Periventricular leukomalacia	6 (32%)
Vasovagal syncope	1 (5%)	Cavum septum pellucidum	4 (21%)
Poor feeding	1 (5%)	Cavum vergae	4 (21%)
Neonatal seizures	1 (5%)	Thinning of the CC	3 (16%)
		VRS enlargement	2 (10%)
		Brain	2 (10%)
		Other anomalies <sup>d</sup>	1 (5%)

- Febrile seizures, infantile spasms, absence, tonic–clonic, and myoclonic seizures have been all associated with SS (Tatton-Brown & Rahman, 2007).
- Furthermore, a wide spectrum of behavioral and emotional disturbances may occur in SS patients, such as ADHD, aggressiveness, irritability, pyromania, social inhibition, psychosis, and autistic features (Mauceri et al., 2000; Tatton-Brown et al., 2005; de Boer et al., 2006).
- The patients with SS reported herein had FS and/or epilepsy.

- Mean age of onset of FS was consistently before the onset of epilepsy (1 year 6 months vs. 5 years 5 months).
- The 64% of SS patients with FS developed epilepsy, a much higher
- Percentage if compared with patients with non syndromic FS (3–5%).
- We noticed that in some of the reported patients the diagnosis of SS was suspected only after they came to our attention for the first seizure, which was febrile in all cases.

- Generalized tonic–clonic seizures were the most frequent type among generalized AF, with a prevalence of 47%. Notably, the 40% of patients had temporal lobe seizures (TLS). Clinical symptomatology of TLS may include olfactory, gustatory, or auditory hallucinations, automatisms, fear, auras (e.g., abdominal aura) with/without behavioral arrest, déjà vu–or jamais vu–like sensations.

- In two patients, TLS presented with abdominal aura and bursts of aggressiveness, thus being initially confused with behavioral disorders.
- Ictal EEG recording allowed for the differential diagnosis between TLS and behavioral problems in these two patients.

- Interictal EEG studies in patients with FS revealed normal background activity or anomalies fitting with the epileptic manifestations.
- Notably, anomalies in the temporal areas were recorded in a majority of patients with epilepsy at interictal EEG.

- Seizures appeared easy to control with the common AEDs at standard doses, such as valproic acid, oxcarbamazepine, carbamazepine, lamotrigine, levetiracetam, topiramate.

- In this case series, monotherapy with valproic acid was the most frequent used treatment. In general, AED administration resulted in progressive reduction and disappearance of seizures.
- Recurrence of seizures required dose correction; only two patients needed polytherapy

- At the time of last follow-up, 4 of 15 epileptic patients discontinued AED therapy (mean seizure-free period: 5 years; seizure-free period range 2–10 years); the other 11 patients still receive AEDs with good clinical control in all cases but one (patient with periventricular nodular heterotopia).

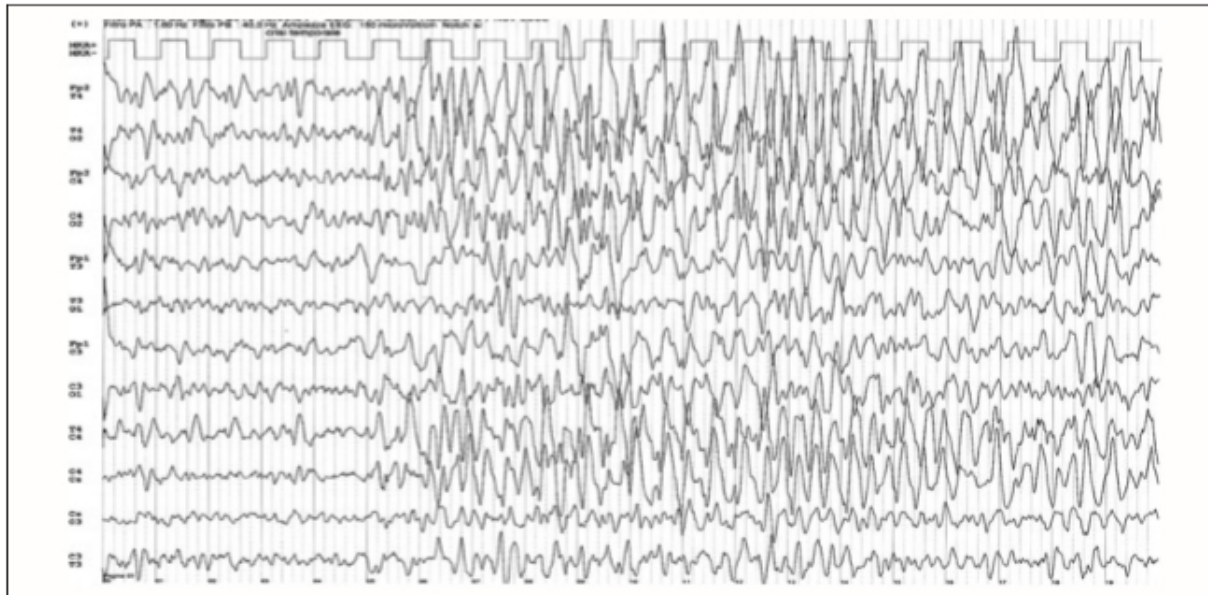
- The pattern of brain abnormalities in SS suggest delayed or disturbed maturation, in particular of midline structures. In a study of 40 SS cases, ventricular anomalies (90%), enlargement of supratentorial extracerebral fluid spaces (70%), and anomalies of corpus callosum (64%) and other midline structures (40%) were the typical findings.

- Periventricular nodular heterotopias were reported in three patients (8%) (Schaefer et al., 1997). In the present series 17 patients had central nervous system anomalies, which were similar to the previous alterations described in children with SS.
- Periventricular nodular heterotopia was observed in one case (5%).
- In general, we found a low incidence of midline brain anomalies compared with the series of Schaefer et al.

- We cannot clarify the reason for the clinical and EEG involvement of temporal lobe in our patients, since no abnormalities were found in the temporal areas by MRI examination.

- Furthermore, studies on the role of the NSD1 gene on the brain (or temporal lobe) development are missing, although it is known that the transcript of the NSD1 gene is expressed in brain tissue (Favarelli,2005).

# Ictal EEG



# Conclusions

- This is the first study investigating the electroclinical features and the long-term follow-up of seizures in patients with SS.
- More than half of FS in these patients evolved to epilepsy.

# Conclusions

- Generalized tonic–clonic seizures were the more frequent type of generalized seizures, whereas TLS were recorded in the 40% of SS with epilepsy in this series.

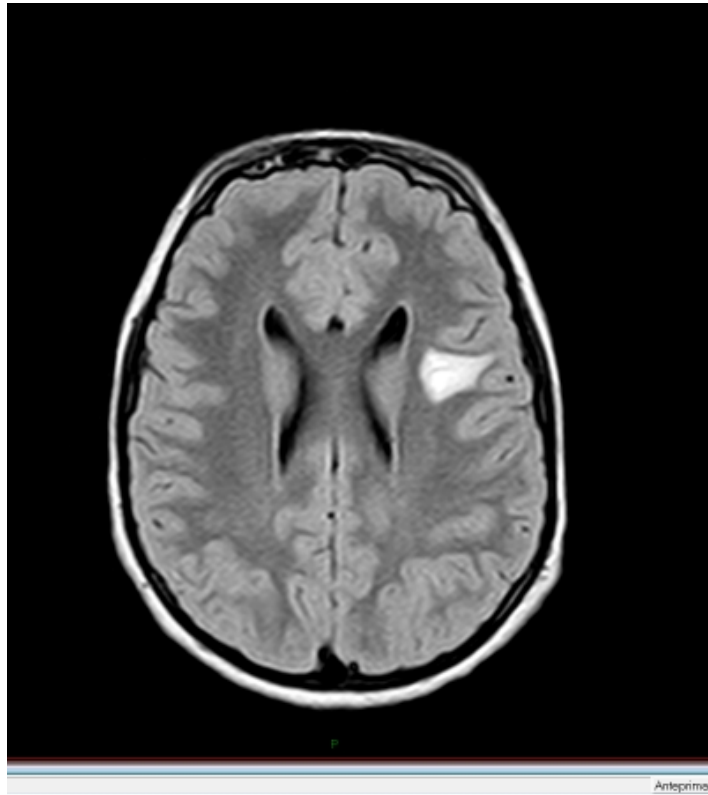
# Conclusions

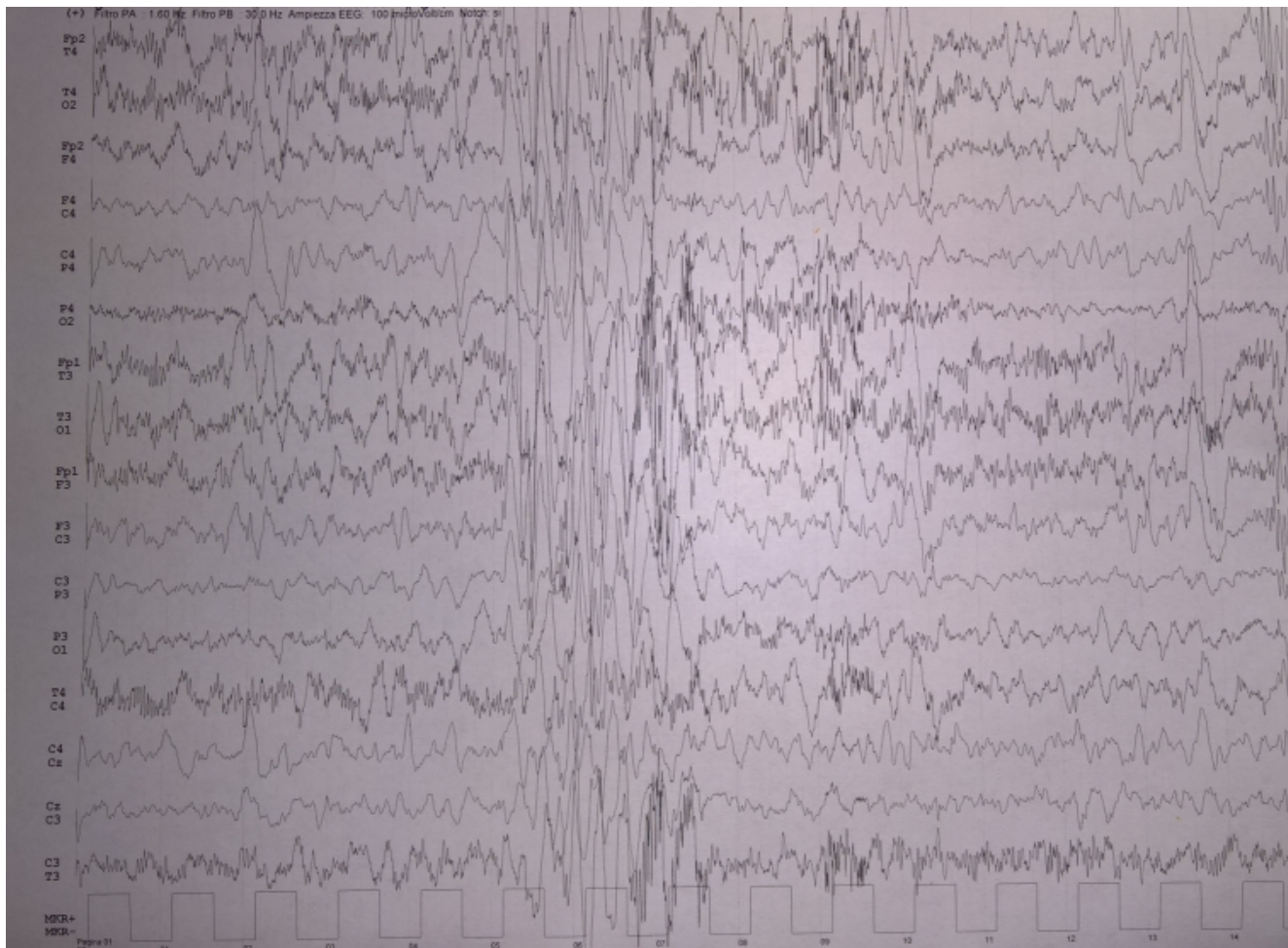
- Because patients with SS may have both behavior disorders and seizures such as TLS, and since TLS may be confused with some behavior disorders, ictal EEG recording may be helpful for differential diagnosis.
- Seizure control seems to be easy to obtain with monotherapy, or, less frequently, polytherapy with AED.
- A careful neurologic evaluation is useful in SS because seizures are an important finding among people with this overgrowth syndrome.

# NEWS

- NUOVI PATTERN RMN ED EEG

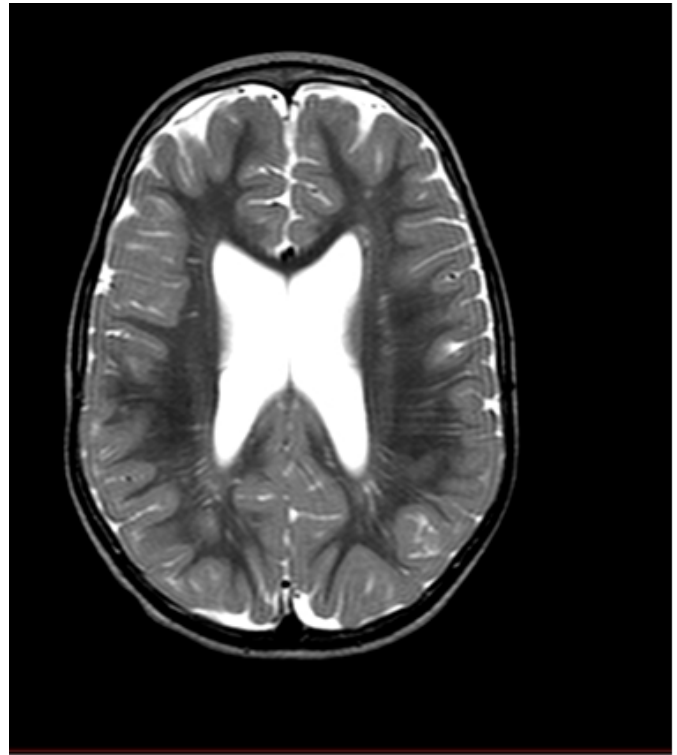
# Rmn







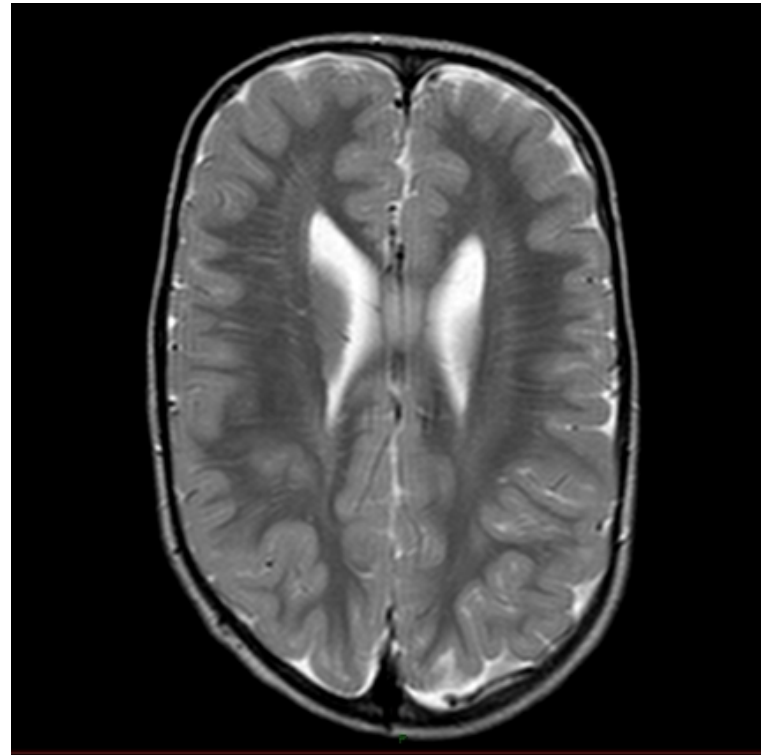
Antepremo 11r



Antepremo 11



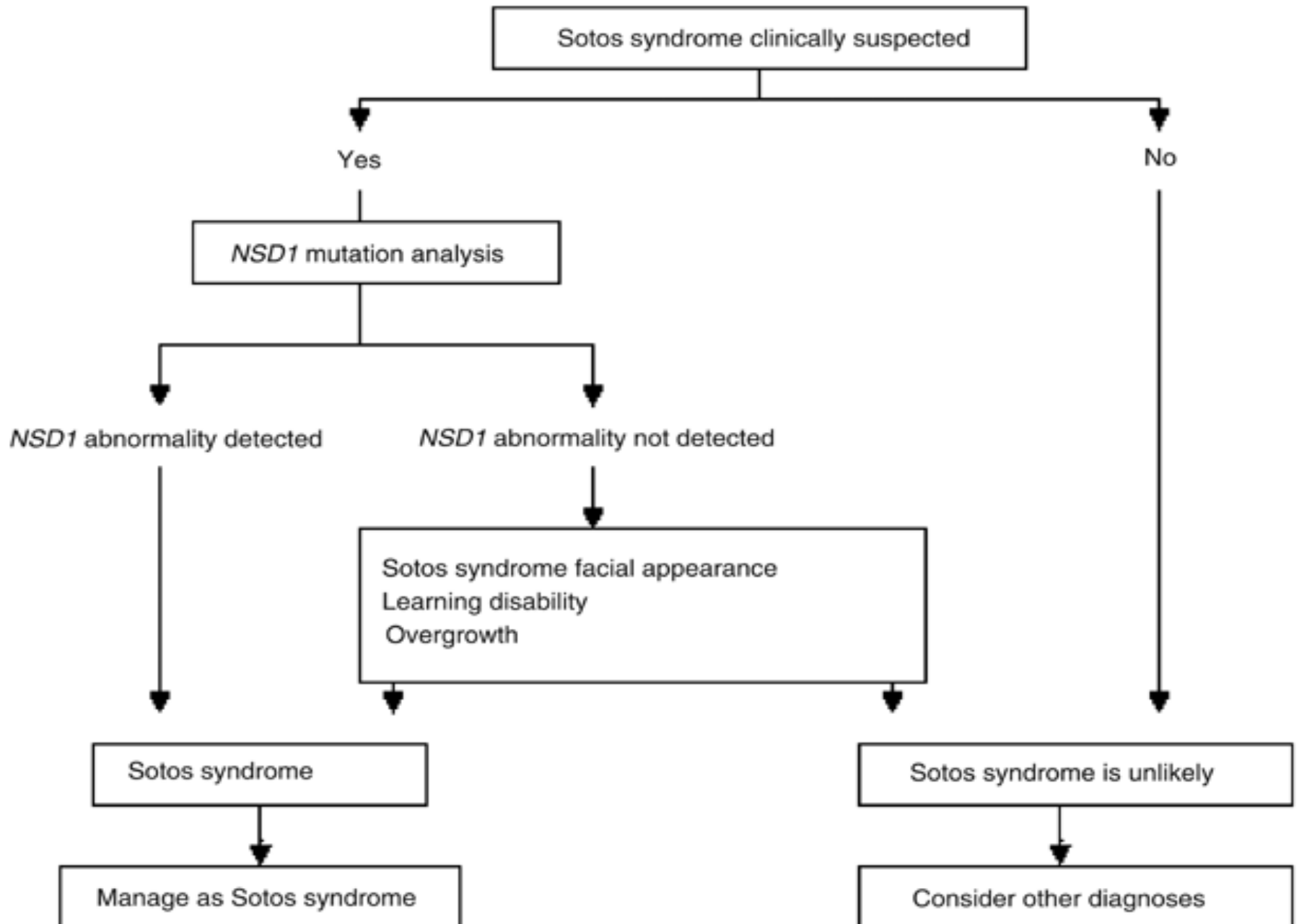
Anteprima



Anteprima



# Diagnostic strategy when diagnosis of Sotos syndrome is suspected.



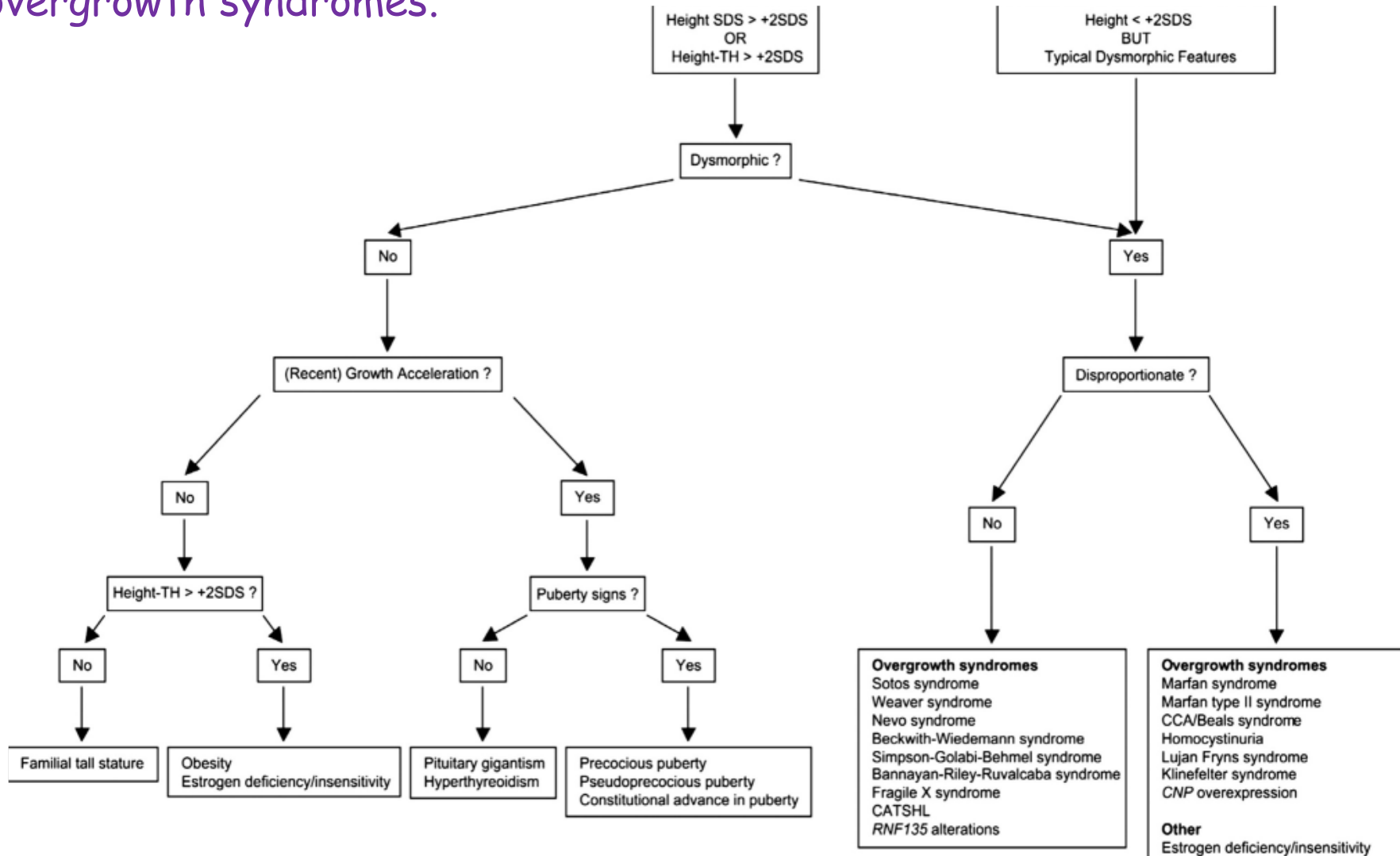
# Diagnosi differenziale

con tutte le condizioni associate a iperaccrescimento:

- Sindr. di Beckwith-Wiedemann
- Sindr. dell' X-fragile
- Sindr. Weaver
- Sindr. Simpson-Golabi-Behmel
- Sindr. Gorlin
- Sindr. Bannayan-Riley-Ruvalcaba

# Diagnosi differenziale

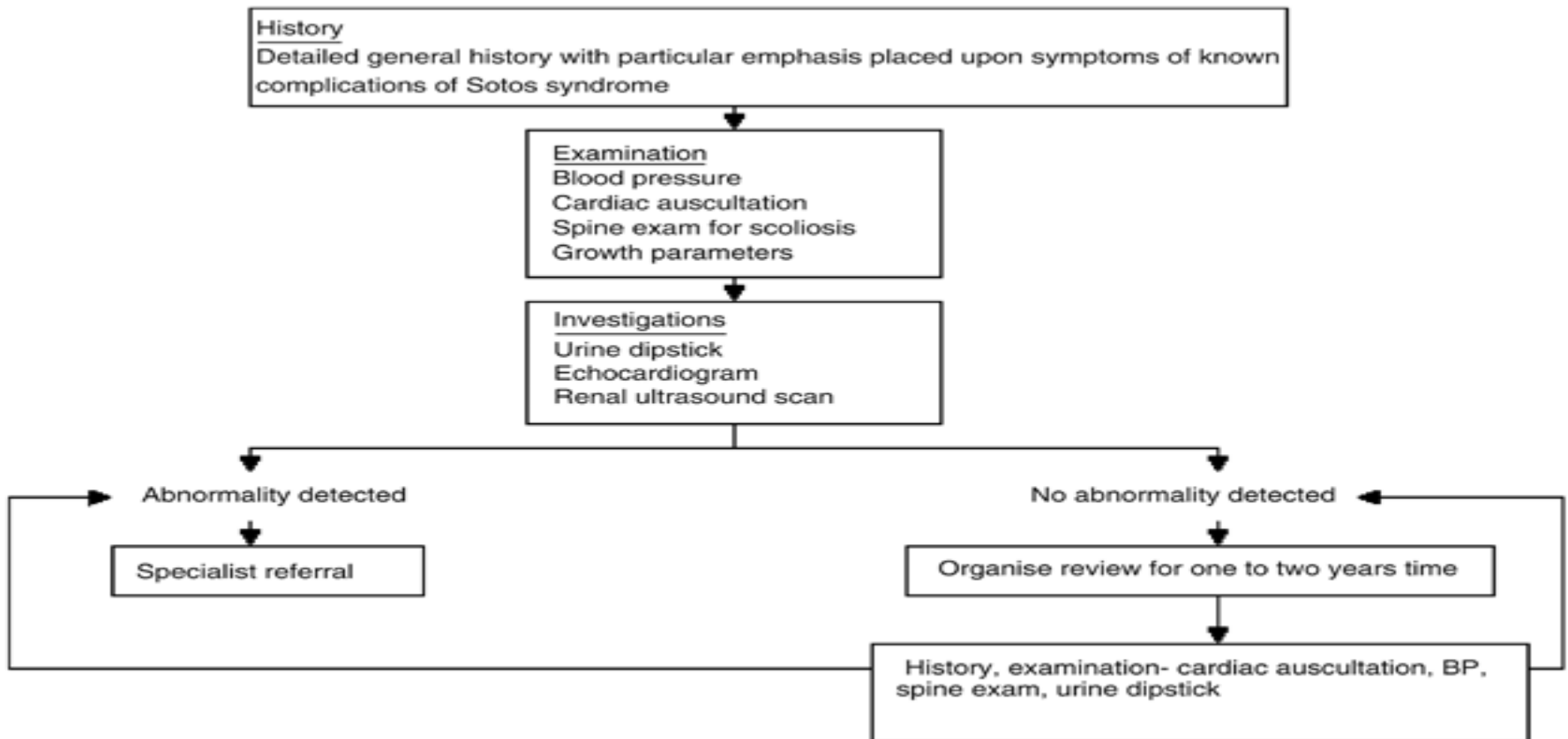
Diagnostic flow chart for the differential diagnosis of tall stature and overgrowth syndromes.



# Trattamento

E' sintomatico ed è rivolto alle patologie associate alla sindrome quali anomalie cardiache, epilessia, scoliosi, reflusso vescicoureterale, etc.

Suggested approach to the evaluation and management of the individuals with Sotos syndrome.



# PROSPETTIVE FUTURE

- CORRELAZIONE GENOTIPO FENOTIPO
- EEG E FUNZIONI COGNITIVE
- NUOVI PATTERN EEG
- FOLLOW-UP
- STUDI MULTICENTRICI