A new mutation of carbonic anhydrase 8 gene expanding the cerebellar ataxia, mental retardation and disequilibrium syndrome (CAMRQ) subtype 3.

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Introduction: Cerebellar ataxia, mental retardation and disequilibrium syndrome (CAMRQ) is a rare genetically heterogeneous autosomal recessive disorder characterized by cognitive impairment, chronic cerebellar ataxia and often quadrupedal gait. This syndrome is composed of four subtypes affecting respectively very low density lipoprotein receptor (VLDLR), WD repeat-containing protein 81 (WDR81), carbonic anhydrase 8 (CA8) and aminophospholipid transporter protein *ATP8A2* genes.

Clinical description: We describe the case of an 11-year-old Syrian girl of whom the consanguineous parents (first cousins) consulted for the development of an ataxic gait from early childhood. On clinical examination, she presented a cerebellar syndrome with dysarthria, trunk and head tremor, intentional tremor, dysdiadochokinesia and enlarged gait. Deep tendinous reflexes and cranial nerves were normal. Babinsky sign was unconsistent and Romberg test was normal. She has walked on all fours until 2 years, with support until 9 years. She currently walks without support for short distances. She presents absence epilepsy well controlled by valproic acid. An IQ evaluation was consistent with mild mental retardation. She performs regular physiotherapy and logopaedics and takes L-carnithine and Quatral®.

Brain MRI with spectroscopy was described as normal (no cerebellar volume loss nor white matter abnormality). Skin biopsy and quadriceps muscle biopsy were normal. Cardiac and abdominal ultrasonography, electrocardiography, electromyography-nerve conduction study were also normal. EEG short and long term were normal. Her ophtalmic exam showed a bilateral astigmatism with a retinitis pigmentosa on ERG. Cerebellar oculomotor syndrome without ocular apraxia neither ocular jerk paralysis were found on video-nystagmography.

We excluded a Friedrich ataxia with a normal sequencing of the Frataxine gene. Liver and renal function tests, thyroid profile, vitamins A,E, K, zinc, free and total carnitine, acylcarnitine profile, abetaliproteinemia, very long chain fatty acids, mitochondrial enzymes, alfafoetoprotein, immunoglobulin profile and sialotransferrine were all in the normal range. Her lipid profile shows a low HDL with normal cholesterol and triglycerides. Apoliporotein A1 was low. Amino acids analysis showed an isolated arginine increase.

After a normal CGH array, a gene panel analysis identified a novel mutation c.251A>G in the carbonic anhydrase 8 (*CA8*) gene on chromosome 8q12.

Discussion: Only two consanguineous families were reported worldwide as affected by a congenital cerebellar ataxia with mental retardation due to CA8 mutation. CA8 is an important regulator of phosphatidylinositol-calcium second messenger system which maintains intracellular calcium homeostasis into Purkinje cells. We expand the neurological phenotype associated with CA8 mutations in light of this new mutation highlighting the originality of this case. We finally

update the pathogenesis of hereditary ataxias due to genetic mutations affecting the calcium balance. Understanding those mechanisms opens new perspectives towards future treatments.

Expanding the phenotype of OPHN1 mutations : 5 unrelated families with intellectual disability and absence of cerebellar hypoplasia.

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Abstract

The oligophrenin I gene (OPHN1, MIM #300127) is located on Xq12 and encodes a Rho-GTPase-activating protein involved in the regulation of the G-protein cycle. Rho protein members play an important role in dendritic growth and in plasticity of excitatory synapses. Mutations in OPHN1 have been identified in patients with X-linked intellectual disability (XLID) associated with cerebellar hypoplasia and ventriculomegaly, suggesting a recognizable syndromic intellectual disability. Patients often share other clinical findings such as seizures, strabismus, ataxic gait, behavioral difficulties and slight facial dysmorphism with a long face, deep set eyes with pronounced infraorbital creases, short philtrum and prominent chin.

We report on five unrelated families affected by mild to severe intellectual disability due to OPHN1 mutations where brain MRI did not reveal any cerebellar anomaly. We describe clinical, genetic and neuroimaging data of affected patients. We discuss the intrafamilial clinical variability and compare our patients with those previously reported. We emphasize the power of next generation techniques (X-exome sequencing, whole-exome sequencing and/or targeted multi-gene panel) to expand the phenotypic and mutational spectrum of XLID caused by OPHN1.

DYT1-Dystonia: How do patients compensate for dystonic postures ? A case report

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DYT 1Dystonia or Oppenheim's dystonia is a form of early- onset isolated dystonia (1) that appears during childhood (2). This autosomal hyperkinetic disorder (2) is usually caused by a 3bp (GAG) deletion of in the *TOR1A (DYT1)* gene, on the chromosome 9q 34 (1-3); however with a penetrance of just 30% - 40% suggesting that additional genetic and /or environmental factors contribute to phenotype expression (4).

A case of a primary torsion dystonia in a 7-year-old patient without any previous history of neurological disease will be discussed. The patient was referred from the department of orthopedics to the consultation of pediatric neurology. He presented for one month walking difficulties, with an initial focal distribution of symptoms involving the left leg. He was initially treated with a walking boot for what was initially diagnosed as an ankle sprain. The patient was intellectually normal. On neurological examination, dystonia was mainly expressed with a steppage gait: excessive flexion of the limb and the knee, associated to a left foot inversion. Furthermore, standard ophthalmic exam and EEG recording were normal. Brain MRI doesn't show focal cortical dysplasia or abnormalities of basal ganglia. CSF analysis tests showed normal concentrations of proteins, glucose and neurotransmitters as well as other para-clinical features like amino acid plasma concentrations and the organic acid analysis in urine. Molecular genetic analysis revealed a heterozygous deletion C.907-909 del GAG in *TOR1A* gene, suggesting a diagnosis of a sporadic early onset dystonia with asymptomatic relatives.

Treatment options are multiple. We started a treatment with low doses of Prolopa, without significant improvement, the same being observed with anticholinergic medication « Trihexyphenidyl Hydrochloride » that proved to be inefficient. Despite a progression of dystonia to the right leg, this patient kept independence in displacements using « tricks » that will be presented and discussed. Deep brain stimulation (DBS) at the Globus Pallidus pars internus (GPi) is an effective treatment for some patients with medically refractory torsion dystonia(4). Children and adolescents possessing the DYT1 gene mutation may respond best of all (4). The proper timing of DBS surgery remains a controversial issue. Accumulating data suggest that the earlier one intervenes with DBS, the better the outcome, especially in DYT-1 (5). Parents of this patient are currently against the introduction of "deep brain stimulation", which should normally be started as soon as possible because of the prognosis.

Early age of onset in the legs predicts a more severe clinical course like development of a generalized dystonia (1- 6), Genetic counseling is highly recommended in this case. Although some specific therapeutic interventions are now available and validated, their acceptance remains difficult and requires a long lasting family guidance process.

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Dystonie de type 11.

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La dystonie de type 11 (Myoclonus-Dystonia) est un trouble du mouvement caractérisé par l'association de contractions musculaires brèves, rapides (myoclonies) et de mouvements répétitifs et soutenus de torsion ce qui induit une posture anormale (dystonie). La maladie débute habituellement avant 20 ans. La transmission est autosomique dominante avec mutation du gène de l'Epsilon-Sarcoglycan. Habituellement, le gène hérité de la mère n'est pas exprimé alors que celui hérité du père l'est. La transmission du gène est donc soumise à un mécanisme d'empreinte maternelle. La prévalence est estimée à 1/500000 en Europe.

Nous rapportons le cas d'un garçon qui consulte à l'âge de 6 ans en raison d'un phénomène de torsion et de crispation se manifestant dans l'exécution de certaines tâches motrices, avec répercussion sur le graphisme et les gestes requérant une dextérité fine. Cet enfant n'a pas d'antécédent familiaux ni personnels particuliers et il a franchi les étapes du développement psychomoteur normalement avec notamment l'acquisition de la marche à 14 mois. A l'époque, l'examen montrait une certaine raideur dans les mouvements, un électroencéphalogramme et une IRM cérébrale normaux et seule de la rééducation psychomotrice a été instaurée. L'enfant n'a reconsulté qu'à l'âge de 8 ans ½ : en raison de ses troubles moteurs induisant une dysgraphie, ainsi qu'en raison d'un T-DAH, l'enfant avait été orienté vers un enseignement spécialisé pour les enfants présentant des troubles instrumentaux. L'examen clinique actuel montre : d'abondantes secousses myocloniques et de discrets mouvements choréiques prédominant aux membres supérieurs, et des mouvements anormaux s'apparentant à une dystonie tâche dépendante lors de certaines actions, surtout l'écriture (cf vidéo).

La recherche génétique de dystonie de type 11 est revenue positive : hétérozygote pour la mutation pathogène c.344A>G, p. (Tyr115Cys) dans l'exon 3 du gène *SGCE*. La sœur âgée de 6 ans présente la même mutation mais le phénotype est dominé par des manifestations myocloniques. Les parents n'ont pas souhaité être testés.

Plusieurs traitements ont été essayés sans succès : L-dopa, Clonazépam, Primidone. Un essai est en cours avec du Zonégran avec une efficacité qui semble un peu meilleure. Le valproate, le lévétiracétam, le topiramate, les traitements anticholinergiques, le L-5-hydroxytryptophane, la toxine botulique pourraient être envisagés. L'ingestion d'alcool est efficace mais bien sûr non recommandée. La stimulation cérébrale profonde du globe pallidal interne et/ou du noyau intermédiaire ventral du thalamus a montré son efficacité dans certains cas, avec semble t'il une efficacité meilleure pour la stimulation du globe pallidal interne.

Conclusion : la dystonie de type 11 est un trouble du mouvement rare, à début précoce et invalidant. Le diagnostic permet une prise en charge adaptée et améliore la qualité de vie des personnes atteintes.

Rhombencephalitis. 5 years later.

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We present the unusual evolution of a young girl first hospitalised for possible rhombencephalitis. This girl was referred to the Pediatric Intensive Care Unit at the age of 15 months for acute neurological deterioration. Since 1 day, she suffered from mild diarrhoea fever. During the night, the child was found to be irritable, exhibiting disorganised eye movements and global hypotonia. The parents took her to the emergency department of another hospital.

She is the first child of non-consanguineous parents. Her family history was unremarkable; she had unrelated Belgian parents. The pregnancy, delivery, and neonatal period were uneventful. She has normal psychomotor development.

Clinical exam revealed mild fever, normal vital signs and absence of signs of meningeal involvement. Obnubilation, nystagmus, axial and peripheral hypotonia, weak deep tendon reflexes, absence of Babinski sign were the most important neurological features. All the investigations (blood and CSF analyses, brain MRI, electromyography and nerve conduction velocities) showed normal results. She progressively recovers with persistence of mild ataxia.

3 years later, she develops auditory and visual impairment. A new diagnostic procedure was performed.

Early onset genetic encephalopathy with epilepsy: further delineation of genotype-phenotype correlation.

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Objectives: further delineation of genotype-phenotype correlation in patients with early onset genetic encephalopathy with epilepsy (EOGEE).

Methods: We recruited 12 refractory epileptic patients with onset before age 12 months. Patients had metabolic work-up, cranial imaging and genetic analysis.

Results:

Patient N°	Onset	DD/ IQ	Gene	Protein	Seizure type
1	3 mo	<50	SCN1A	p.L1660P	SE,TC, My, R
2	6 mo	54		p.R1319EfsX3	SE, TC, R
3	9 mo	61		p.L1828S	C, TC, SE
4	4 mo	+		p.K1512*	TC, aH, My, SE, R
5	6 mo	86			TC, C, SE, R
6	11 mo	57		p.I880T	TC, C, SE
7	$1^{1/2}$ mo	++	del 2q24.3 (SCN)		SE, TC, My, MP, R
8	1 d	++	SLC13A5	p.W341*/ p.G219R	T, C, My, SE, R
9	6 mo	+	SCN8A	p.R1617Q	TC, SE, R
10	3 mo	+	CDKL5	p.R178Q.	T, C, S
11	3 mo	++	KCNT1	p.G243S/p.G288S	C, TC, SE, MP, R
12*	14 d	++	HCFC1 ATRX	p.A115V p.K910E	T, C, TC, My, SE, R

aH: alternating hemiclonic; C: clonic, d: day; DD: developmental delay; IQ: intellectual quotient; moderate: +; MP: migrating partial; mo: month; My: myoclonia; R: refractory; SCN: sodium channel gene cluster; ++: severe; S: spasm; SE: status epilepticus; T: tonic; TC: tonico-clonic.

Conclusion: EOGEE was associated with both refractory epilepsy and moderate to severe developmental delay. The most frequent mutations occur in *SCN1A*. *KCNT1*, *HCFC1* and *ATRX* mutations and 2q24.3 deletion were associated with severe adverse outcome. In *SLC13A5* mutations, onset occurred at the earliest age.

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Glucose transporter (GLUT1) deficiency syndrome: report of three cases. Illustration of clinical variability and different treatment options.

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Introduction: Glut1 deficiency classically manifests as an early-onset epileptic encephalopathy with developmental delay and complex movement disorders. It is caused by a mutation in the SLC2A1 gene. Genotypic and phenotypic variability is substantial. The first choice of treatment is the classic ketogenic diet. However, modified diets have been proven to be effective as well. Other treatment modalities are under research. We report three patients with GLUT1 deficiency syndrome with a variable presentation, clinically improving with a low glycemic index diet and high-amylopectin corn starch.

Case descriptions: The

first patient presented at the age of 6 years with absences and a global developmental delay. She was treated with lamotrigine, without any effect on absences. At the age of 12 and 18 months, she had an episode of febrile convulsions. At clinical examination there was a dysmetria and a tremor of the upper limbs and there were difficulties with balance. Brain MRI showed periventricular leukomalacia, with no other abnormalities. EEG showed bilateral spike and waves. Anti-epileptic treatment was changed to ethosuximide with good effect on seizures. Gene panel for epilepsy elicited a de novo mutation in the patient's SLC2A1 gene (c.680-2A>G). She is treated with a low glycemic index diet and a high-amylopectin corn starch (Glycosade) with good effect on symptoms.

The second patient presented at the age of 5 years with episodic walking difficulties, that recovered after resting. There were no accompanying symptoms. Medical history was uneventful. Clinical examination didn't show any abnormalities. Brain MRI was normal. EEG showed bilateral spike and waves. There were no clinical seizures. A mutation in the *SLC2A1* gene (c.635G>A) was discovered. This patient also showed clinical improvement with a low glycemic index diet and Glycosade.

Two different mutations in the *SLC2A1* gene (c.766_768del, c.1171G>A) of our third patient were discovered at the age of 19 years, after presenting with involuntary movements after physical effort. She was born preterm, has periventricular leukomalacia on brain MRI and is known with epilepsy, intellectual disability, a hemiparesis and coordination difficulties. She also started a low glycemic index diet and Glycosade.

Discussion and conclusion: Our three patients illustrate the variable clinical spectrum of GLUT1 deficiency syndrome. Treatment with a low glycemic index diet and a high-amylopectin corn starch showed clinical improvement in our patients.

We hope to increase awareness for this treatable disease and discuss other treatment options besides the ketogenic diet.

Intractable hiccup and nausea (IHN): think about AQP4 antibodies !

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Introduction: Sixty to eighty percent of patients with typical neuromyelitis optica (NMO-Devic disease) present autoimmune antibodies (NMO–immunoglobulin G [IgG]) targeted against the aquaporin-4 (AQP4) water channel. The high specificity of AQP4-IgG for NMO has allowed the identification of seropositive patients with atypical presentations of the disease: NMO spectrum disorders (NMOSD). In NMO/NMOSD patients, cervical myelitis extending to the medulla oblongata can cause intractable hiccup and nausea (IHN), also called area postrema syndrome. In this case report, we illustrate that in the presence of IHN associated with lesion in the area postrema, AQP4-IgG should be tested, as it may reveal a NMOSD and change the medical treatment.

Case presentation: A previously healthy 14-year-old girl presented several episodes of persistent hiccups with nausea and vomiting during five days that resolved spontaneously. Two weeks later, she became ataxic with dysphonia and swallowing difficulties. She presented fever (40°C) and her general practitioner started an antibiotic treatment. Her condition got worse, she was diagnosed a severe infectious pneumonia and hospitalized to receive IV antibiotics. As she presented a multidirectional nystagmus with blurred vision, paresthesias of both feet and left hand, brain MRI was performed and revealed bulbar myelitis in the area postrema region without supratentorial lesion or optic neuritis. Breathing difficulties got worse and she required mechanical ventilation. Lumbar puncture revealed lymphocytic pleocytosis. Visual evoked potential, medullar MRI and infectious work-up were inconclusive. A treatment with IV immunoglobulin was initiated with slight improvement. Because of the presence of IHN and area postrema lesion on brain MRI, Anti-AQP4 antibodies were tested and came back positive in serum and cerebrospinal fluid. NMOSD was diagnosed and she received methylprednisolone pulses (20mg/kg/day for three days) followed by oral taper of prednisone (starting with 1.5 mg/kg/d) for 3 months. Two weeks after starting steroids, she received azathioprine to prevent relapses. After 3 months, motor and sensory functions are normal but she still requires nocturnal ventilation due to hypoventilation during sleep and has a decreased nausea reflex. Control MRI showed that lesions in the area postrema region have decreased.

Conclusions: This case report illustrates that in the presence of IHN associated with brain lesion in the area postrema, AQP-4 IgG dosage should be performed in order to exclude NMOSD, a disabling and relapsing disease, and to give appropriate treatment that may decrease the frequency and the severity of the relapses.

Vitamins, minerals, micronutrients:Do they play important role in epilepsy triggering and treatment?

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Introduction: The role of vitamins and micronutrients in epilepsy etiology and treatment is generally well-known, but also still "open" for further research. Although such relative cases are uncommon, they are a curable part of intractable epilepsies, so early suspicion, prophylactic strategies and prompt decisions are the conditions of initiating proper treatment and preventing neurological damage.

Purpose: To review and update the usage of vitamins and minerals in children with epilepsy, the causes of disorders, the available evidence and the clinical decision making.

Material-Methods: Contemporary bibliography review and evidence questing.

Results-Conclusion: Before any recitation, we should recall the blood-brain- barrier (BBB): One vitamin's levels can be normal peripherally but low into the brain, and also sometimes high supplementation doses are needed just for the BBB overtaking. Disorders can be due to dietary causes, as well as genetic, autoimmune or drug-induced. Until now, Pyridoxine, Pyridoxal 5 Phosphate, Folic Acid in its various forms, Biotin, Vitamin B12 and B1 have been proved as involved in seizures mechanisms and management, as well as Glucose, Sodium, Calcium and Magnesium. Rarer cases are related with Copper, Zinc and Manganese. There is also discussion about vitamins D and E, which have a role in encephalopathy and epilepsy whole management, but not -at least until nowadays- as primary associated with epileptogenesis itself. Vitamin K gets value in newborns whose mothers take certain antiepileptic drugs. Some rare metabolic errors potentially causing epilepsy can be treated micronutrients or sole proteins.

There are many references in bibliography and publications for numerous nutrients as being involved in epilepsy, most of them come from anecdotal cases or alternative sources, with insufficient evidence.

Resuming the data, some original practical algorithms will be presented, proposing decision making process according to the different ages of children.

TuberOus Sclerosis registry to increase disease Awareness (TOSCA): Baseline Data for the Belgian Cohort

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Background: The TuberOus SClerosis registry to increase disease Awareness (TOSCA) is an international database designed to address knowledge gaps in the natural history and management of Tuberous Sclerosis Complex (TSC). To understand the presentation and management of this rare autosomal dominant genetic disorder in Belgium, we reviewed the Belgian baseline data.

Methods: We selected the data of all patients included in TOSCA through one of the 16 Belgian sites. Mutation analysis, neurological, neuropsychological, nephrological, cardiological, pneumological and dermatological symptoms and complications, and their different treatments were registered. Patients receiving mTOR inhibitors through participation in a clinical trial or medical need program were excluded from TOSCA as of Protocol Amendment 1 (dd 3/12/2012).

Results: Out of the 2216 international patients on whom baseline data are available, 110 were included in Belgium. Mean age of TSC diagnosis in the Belgian cohort was 7.4 years (median 2.0 years, range 0-59 years). In 6 patients (5.5%) diagnosis was made prenatally. In 92 (83.6%) molecular genetic testing was performed. A mutation in TSC1 or TSC2 was identified in 20.7% and 50% respectively. In 29.3% no mutation was identified (NMI). Structural brain lesions included cortical tubers in 100 (90.9%), subependymal nodules in 85 (77.3%), white matter abnormalities in 37 (33.6%) and SubEpendymal Giant cell Astrocytoma (SEGA) in 22 (20.0%). The mean age of SEGA diagnosis was 6.4 years (median 5.0 years) and the mean time since the previous scan was 2.1 years (median 1.0 year). 8 (36.4%) patients with SEGA were treated: 5 underwent surgery, 1 received an mTOR inhibitor and 2 were treated with a combination of both therapies. Epilepsy was present in 88 (80.0%), 71.6% of which had focal seizures and 37.5% had infantile spasms. Seizures were controlled in 28 patients (84.8%) with infantile spasms, in 32 patients (52.5%) with focal seizures and in 20 patients (62.5%) with other seizure types. Only 36 children (32.7%) had formal neuropsychological assessment. Of these, 50.0% had IQ scores within the normal range. Behavioral problems were reported in 72 (65.5%). Other psychiatric diagnoses included ASD in 37 patients (33.6%), ADHD in 26 patients (23.6%), depression in 13 patients (11.8%) and anxiety disorder in 6 patients

(5.5%). Formal evaluation for ASD, ADHD, depression and anxiety disorder was performed in 17, 5, 2 and 1 patient respectively. Nephrological features included angiomyolipoma in 55 (50.0%), most of them asymptomatic (86.8%), renal cysts in 48(43.6%), polycystic kidneys in 10 (9.1%), renal malignancy in 4 (3.6%) and impaired renal function in 4 (3.6%). In 50 patients (45.5%) imaging was repeated after a mean interval of 1.9 years.Cardiac rhabdomyoma was present in 36 (32.7%) and lymphangioleiomyomatosis in 6 (5.5%). The most common dermatological features were ≥3 hypomelanotic maculae in 73 patients (66.4%) and facial angiofibromata in 72 patients (65.5%). Retinal hamartoma were seen in 23 patients (20.9%) and liver hamartoma in 11 (10.0%).

Conclusion: TOSCA is the largest clinical database of TSC patients with a detailed description of clinical features. Although most of the Belgian data were comparable with the international data, some differences were noted. Since mTOR inhibitors became commercially available in Belgium only after enrolment in TOSCA was closed, it was impossible to compare treatment with mTOR inhibitors between the Belgian and international groups. The median age at SEGA diagnosis was earlier in the Belgian cohort (5.0 years) compared to the international cohort (8.0 years), suggesting regular monitoring for possible emergence of SEGA in children.In the Belgian cohort, molecular genetic testing was performed more frequently (83.6%) compared to the international cohort (43.1%), enabling more appropriate genetic counseling. The proportion of prenatally diagnosed cases was similar. In both cohorts there was a striking underassessment of TSC-associated neuropsychiatric disorders (TAND). These data therefore call for adherence to the international recommendations of yearly screening for TAND complemented by formal multidisciplinary evaluation at times of transition or on indication. In line with the international cohort, epilepsy was present in approximately 80% of patients, and almost half of the patients with focal seizures were refractory to treatment. This highlights the need for additional treatments for epilepsy in TSC. The EXIST-3 study has demonstrated the contribution of mTOR-inhibitors in this indication and additional trials are under way.

Baseline Patient Demographics for Overall Cohort and Belgian Sub-cohort

Characteristics	Overall Cohort (N = 2093)	Belgian Sub-cohort (N = 110)
Median age at consent (years)	13	14.0
Median age at diagnosis (years)	1	2.0
Gender Male Female	 1009 (48.2%) 1084 (51.8%)	 55 (50%) 55 (50%)
Molecular testing, n (%)	902 (43.1%)	92 (83.6%)
Genetic testing, n (%) No mutation identified TSC1 mutation only TSC2 mutation only Both TSC1 and TSC2	 125 (13.9%) 178 (19.7%) 571 (63.3%) 5 (0.6%)	 27 (29.3%) 19 (20.7%) 46 (50%) 0
TSC inherited from 1 parent	290 (14%)	15 (13.6%)
Patients with prenatal diagnosis	124 (5.9%)	6 (5.5%)

Overall manifestations of TSC in TOSCA participants

TSC manifestations	International data, % (N = 2216)	Belgian data, % (N = 110)
Cortical tubers	83	90.9
SEN	78.9	77.3
SEGA	25	20
White matter abnormalities	20.5	33.6
Epilepsy	83.6	80
Behavioral problem	37	65.5
Intellectual disability	12.3	11.3
(sev+prof)	9.7	5.5
Anxiety	6.1	11.8
Depression	21.1	33.6
ASD	19.1	23.6
ADHD		
LAM	7.1	5.5
Renal AML	48.3	50
Multiple renal cysts	24.2	43.6
Retinal hamartoma	14.4	20.9
Retinal achromic patch	2.4	1.8
Cardiac rhabdomyoma	35.8	32.7
Facial angiofibroma	58.8	65.5
Forehead plaques	14.3	6.4
>3 hypomelanotic maculae	66.6	66.4
Shagreen patches	27.9	33.6
(Peri)ungual fibroma	17.5	19.1
Confetti lesions	8.4	4.5