Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome

(English version)

Perinatal period		
	Description	**Special problems and their management**
Respiratory difficulties	They frequently require Neonatal ICU, mainly due to the need for respiratory assistance during the perinatal period that varies from oxygen therapy to invasive mechanical ventilation, ranging from a few hours of support to a few months. Laryngeal stridor, glossoptosis, tracheomalacia, and pulmonary hypoplasia have also been reported.	NICU. Mechanic ventilation. Evaluation by **otorhinolaryngologists** and **pulmonologists** to rule out anatomical abnormalities is essential. Respiratory support from **oxygen therapy** to **invasive mechanical ventilation** and need of tracheostomy.
Feeding difficulties	Feeding difficulties with frequent episodes of choking or ineffective sucking are very common. The combination of hypotonia, lethargy, dysphagia, and a high palate can make oral feeding very difficult to achieve.	**Nutritionists** and **dysphagia specialists** are needed. An anatomical evaluation to rule out **malformations** is necessary. Supportive nutritional intervention may be necessary, ranging from a nasogastric tube to a permanent gastrostomy or parenteral nutrition.

Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome

Perinatal period		
	Description	**Special problems and their management**
Contractures	Clubfoot, arthrogryposis, contractures, and other joint movement restrictions are frequently present at birth. Fetal hypokinesia can lead to severe arthrogryposis.	Early intervention through orthopedics may be essential to ameliorate the prognosis. It is important to refer to specialists on **rehabilitation** and **children's orthopedics**.
Hormonal problems	Several endocrine abnormalities have been detected during the perinatal period, including diabetes insipidus, hyponatremia, growth hormone (GH) deficiency, hypoglycemia, and hypocalcemia (see Endocrinology section).	Blood **glucose** levels need to be controlled during the perinatal period. Laboratory tests at this age should include a comprehensive analysis of **ions, glucose, and hormones** to rule out frequent abnormalities. Refer to the pediatric **endocrinologist**.
	In the perinatal period, an evaluation by a child neurologist and a geneticist/dysmorphologist is recommended. A detailed physical examination and a standardized protocol are recommended to rule out congenital malformations that include echocardiogram, abdominal ultrasound, cranial ultrasound...	

Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome

Childhood and Adolescence		
SPECIALTY	**STUDIES AND FOLLOW-UP**	**SPECIFIC CARE AND RECOMMENDED STUDIES**
Endocrinology (E)	Every 6 months/ Physical exam Assessments: Laboratory Ultrasound Neuroimaging (MRI)	E1 **Failure to thrive** during infancy and childhood, but also excessive increase in weight, trend to obesity, and hyperphagia beginning after infancy. Dietary intervention may be necessary. E2 **Short stature** (-1.5 SD to -5 SD), sometimes GH may be needed (consider the increased risk of obstructive apnea when prescribing GH). E3 **Diabetes insipidus** has been described presenting with polyuria, low urine density, hyposthenuria, and hypernatremia. Hormone replacement therapy may be required. E4 **Panhypopituitarism** caused by pituitary gland hypoplasia has been described, but also with normal MRI. It is necessary to monitor thyroid function, somatomedin C, GH, adrenal hormones, testosterone, LH and FSH. Hyperprolactinemia has been detected. Hormone treatment, including GH, levothyroxine, and hydrocortisone, may be necessary. Hormone replacement therapy. Adolescence → estrogens. E5 **Hypoglycemia**. Guarantee the intake and maintenance of glucose. Rule out hyperinsulinemia. E6 **Temperature** instability. Support measures. E7 Hypoplastic genitalia, micropenis and cryptorchidism. Assess testosterone, surgery.

Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome

Childhood and Adolescence		
SPECIALTY	**STUDIES AND FOLLOW-UP**	**SPECIFIC CARE AND RECOMMENDED STUDIES**
Gastroenterology (G)	Every 6 months/ Physical exam Feeding Observation Assessment: pHmetry Video fluoroscopy Image (Rx) Laboratory	G1 **Feeding** problems are almost constant. Initial feeding difficulties are due to dysphagia, recurrent respiratory aspiration, and sometimes a nasogastric tube and gastrostomy are required. G2 Early-onset chronic **constipation** and **gastroesophageal reflux** are also common. G3 Infrequently reported complications: Intestinal pseudo-obstruction, velopharyngeal insufficiency, eosinophilic esophagitis, and food allergies.
Muscular and skeletal (MS)	Every 12 months/ Physical exam Assessment: Image (Rx) Electromyogram and nerve conduction	MS1 Abnormal muscle tone is very frequent, especially hypotonia. MS2 **Arthrogryposis** is very common: contractures, shortening of limbs, elbows, knees, hips. Camptodactyly, clinodactyly, brachydactyly of the fingers, adducted thumbs. MS3 **Club feet** and **equinovarus** feet have been repeatedly described. MS4 **Scoliosis**, kyphosis, lordosis and asymmetric chest. Early rehabilitation programs and external bracing may be needed. Periodic X-ray monitoring of the hip in children who cannot walk and images of the spine X-ray as a whole is recommended. Consider surgery if necessary. MS5 Less frequently: mesomelic and rhizomelic shortening of the limbs, hip dysplasia, and distal muscular atrophy of the limbs.

Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome

Childhood and Adolescence		
SPECIALTY	**STUDIES AND FOLLOW-UP**	**SPECIFIC CARE AND RECOMMENDED STUDIES**
Neurodevelopmental problems and intellectual development (ND)	Every 6-12 months Physical exam Assessment: Scales and developmental assessments either on the patient or completed by the parents	ND1 Abnormal muscle tone and **arthrogryposis** are very common. Hypotonia is the most prevalent. ND2 **Gross motor development** may be severely impaired by delayed acquisition of head control, sitting position, and gait (not achieved by many patients). ND3 **Fine motor development** is also atypical due to motor abnormalities, arthrogryposis, and camptodactyly. The purposeful use of the hands, which is based on cognition and social skills, may be impaired. Rehabilitation programs, early stimulation and, later, occupational therapy programs are essential. ND4 **Social skills** and communication are often severely affected. Only some of the patients can develop, speech and language (generally poor). ND5 **ASD traits and behavioral abnormalities** are very frequent and can interfere with communication skills. Evaluation by speech therapists is recommended. Alternatives to oral communication, such as pictographs or electronic devices, can be of help. Psychotherapy may be necessary for patients with ASD, to treat not only the communicative difficulties but also rigidity, repetitive behaviors, hypersensoriality,...

Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome

Childhood and Adolescence		
SPECIALTY	**STUDIES AND FOLLOW-UP**	**SPECIFIC CARE AND RECOMMENDED STUDIES**
Epilepsy (E)	Every 12 months Clinical interview Assessment: EEG	E1 Febrile seizures have been reported. E2 Epilepsy was found in less than 50% of patients, including different types of seizures (partial, generalized). Different AEDs were used successfully.
Neuroimaging (NI)	At the time of diagnosis. Afterwards, neuroimaging studies if new symptoms are present: MRI	NI1 Delayed myelination, ventricular enlargement, abnormalities of the corpus callosum (thinning, dysplasia or agenesis). NI2 Normal or hypoplastic pituitary gland is frequently reported. NI3 Rarely described: global cerebral atrophy, increased T2 signal in the caudate nucleus or putamen, globus pallidus, hypoplastic vermis, localized cerebellar hemorrhages.
Sleep disorders (SD)	Every 12 months Assessment: Sleep questionnaires Polysomnography (PSG)	SD1 Central and/or obstructive apnea have been reported and can worsen the cognitive and behavioral phenotype, as well as can be the cause of premature death. Periodic PSG is recommended.

Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome

Childhood and Adolescence		
SPECIALTY	**STUDIES AND FOLLOW-UP**	**SPECIFIC CARE AND RECOMMENDED STUDIES**
Infections (I)	Every 12 months Assessment: Laboratory Lung imaging studies	I1 **Recurrent respiratory infections** have been reported in patients with respiratory assistance but also without respiratory support. Chronic lung disease has also been reported due to repeated bronchopneumonia or recurrent aspirations. Imaging studies may be required to evaluate the lung parenchyma and rule out malformations. Invasive studies are rarely necessary. I2 No predisposition to infections in other organs or systems is reported.
Cardiology (C)	At the time of diagnosis and if new symptoms develop Physical exam Assessment: ECG Echocardiography	C1 **Septal defects (CSA)** have been reported as the most common structural cardiac defects, sometimes solving spontaneously. C2 Bradycardia has been described in a 1-month-old baby.
Ophthalmology (O)	Every 12 months Physical exploration Assess: Acuity assessment Fundus Imaging techniques	O1 **Strabismus** and **nystagmus** have been described as oculomotor disorders. O2 Refractive errors have been reported. O3 Hypoplasia or atrophy of the optic nerve can be present. O4 Vision is usually difficult to assess in patients with SYS. Pediatric ophthalmologists are required. Lack of eye tracking has been described, however probably features of ASD underlie the abnormal ocular pursuit. O5 Rare: Xerophthalmia, caused by sleep with opened eyes.

Supplementary Table 2: Management and surveillance proposed protocol for Schaaf-Yang Syndrome