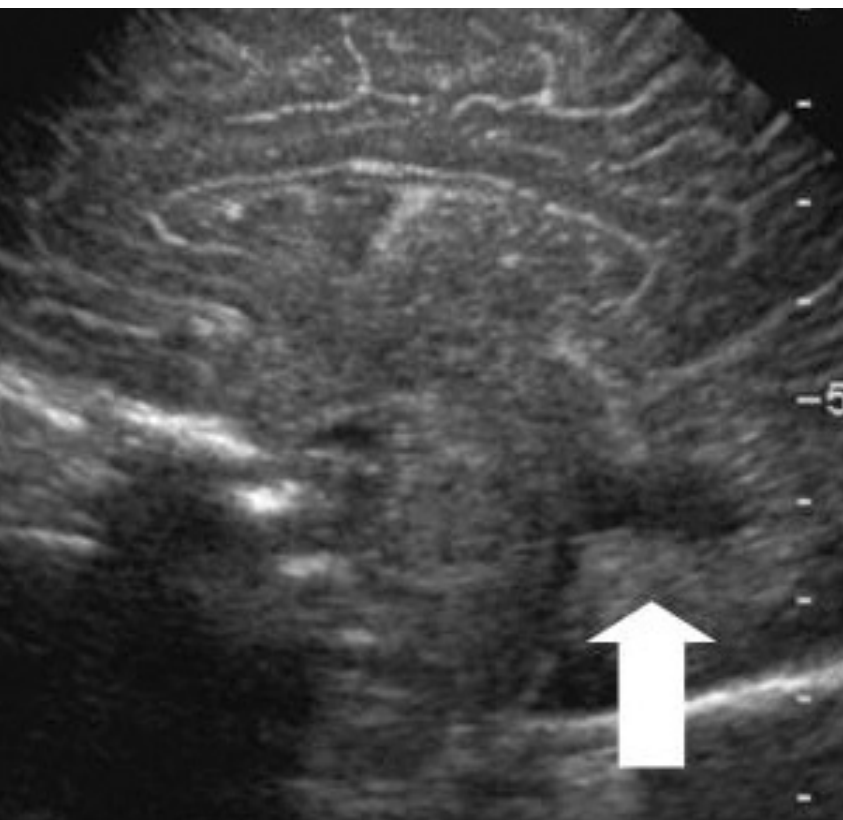


A term infant with episodic
tachypnea and apnea

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This 2690 g female infant had been delivered spontaneously at 40 6/7 weeks of gestation after a normal pregnancy and presented with tachypnea at the age of 10 hours. Respiratory support with nasal CPAP was required for a few hours. Chest X-ray and blood tests on admission were normal.

On the second day, there was an abnormal respiratory pattern with episodic tachypnea with frequencies up to 180 breaths per minute and central apneas during sleep. Apart from the irregular breathing pattern, the newborn also had ptosis of the right eye, general muscular hypotonia and a soft occipital tumor measuring about 1 cm in the diameter. Because of the irregular breathing pattern a provisional diagnosis of Joubert Syndrome (JS) was made.

Cerebral ultrasound showed an absent or markedly hypoplastic cerebellar vermis, an abnormally shaped fourth ventricle (Fig. 1) and an occipital meningocele. The MRI revealed in addition dysgenesis of the corpus callosum, signal alterations of the brainstem and the cranial nerve nuclei and a molar tooth sign (deep interpeduncular fossa, narrow isthmic region, thickened superior cerebellar peduncles, aplastic/hypoplastic cerebellar vermis). The latter is known to be pathognomonic for Joubert Syndrome (Fig. 2, 3). During polygraphy, a pathological cardiorespiratory regulation with the typical episodic tachypnea and apnea, appearing mainly during REM-sleep, was found (Fig. 4).

Abdominal ultrasound demonstrated an abnormal signal in the renal parenchyma without cortico-medullar differentiation including a few renal cysts. Serum creatinine and urea were normal. The ophthalmological examination showed no abnormality apart from the ptosis of the right eye.

At the age of two weeks, the episodic tachypnea had partially resolved, but apneas during sleep were still present. Therapy with caffeine citrate was not effective. Because of the persistence of apneas home monitoring was initiated.

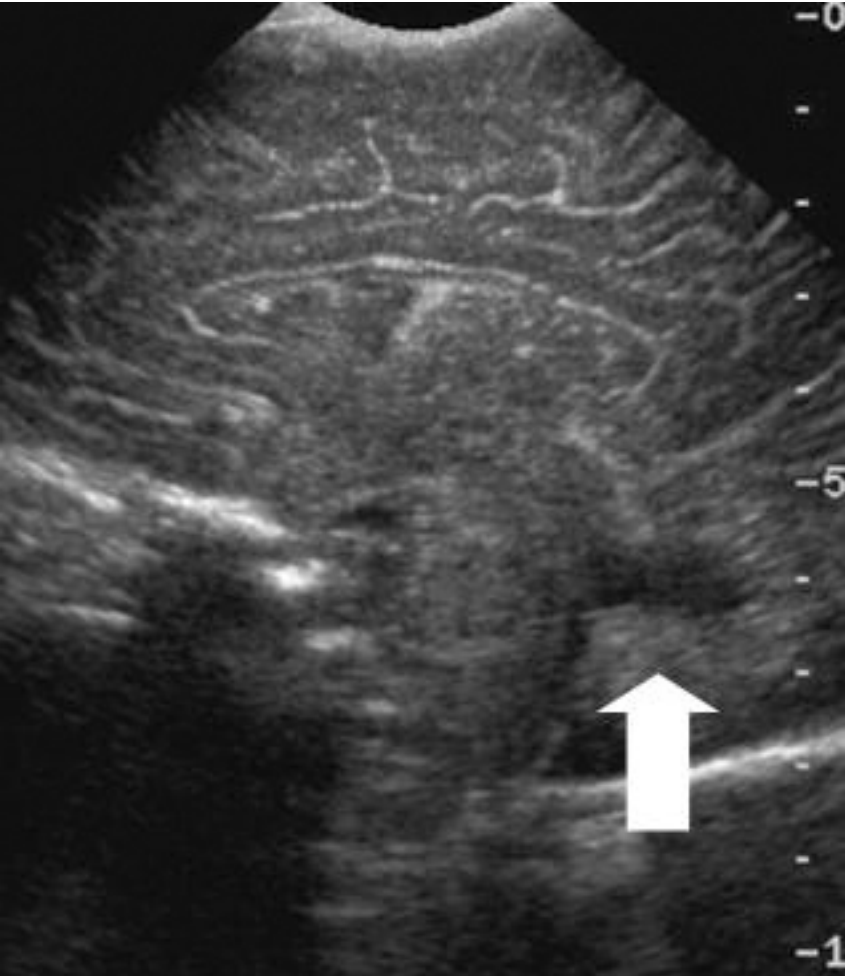


Fig. 1

Parasagittal US showing enlarged 4th ventricle.

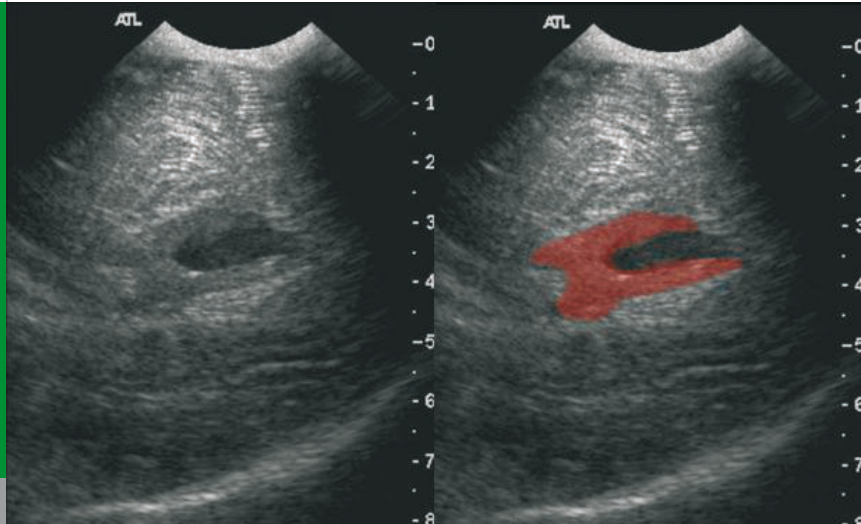
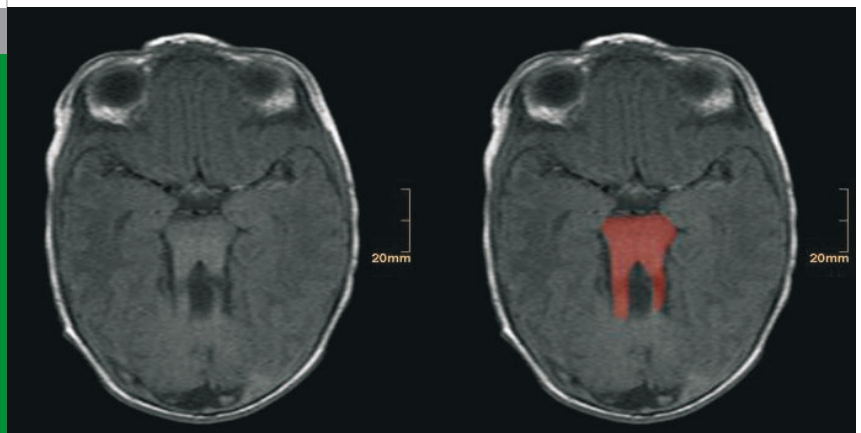


Fig. 2

Coronal US showing the characteristic molar tooth sign.

Parasagittal MRI showing the characteristic molar tooth sign.

Fig. 3



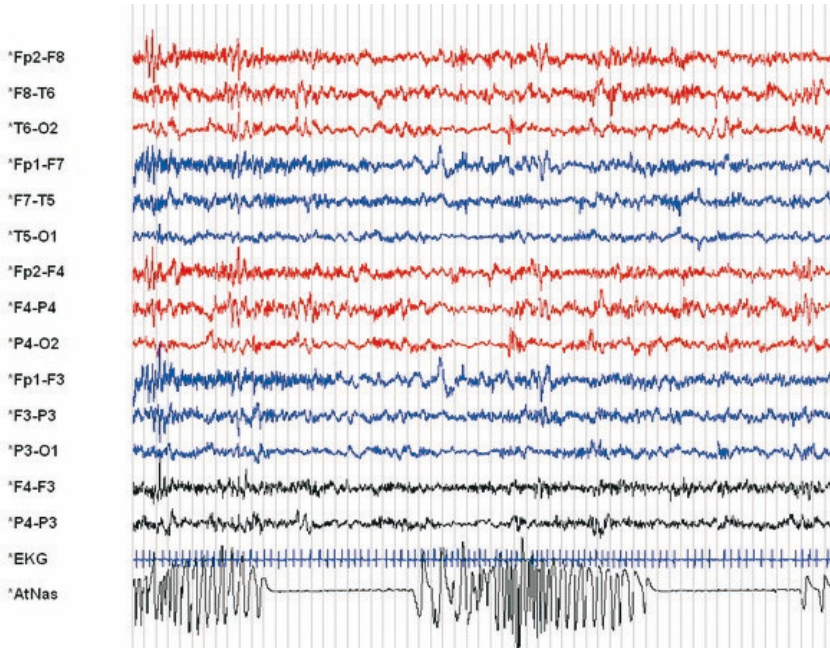


Fig. 4

Polygraph showing normal electrical activity but abnormal respiratory pattern (see AtNas).

DISCUSSION

JS is a rare autosomal recessive disease which manifests with episodic tachypnoea/apnoea, muscular hypotonia, abnormal eye movements and developmental delay. Diagnosis is based on the demonstration of malformations of the cerebellum (aplasia/hypoplasia of the vermis) and the brainstem. There are only about 100 cases reported in the literature. Apart from the cardinal symptoms already mentioned, additional pathologies can be found in individual cases (hepatic fibrosis, hydrocephalus, polydactyly, renal cysts etc.), suggesting that JS itself represents a genetically heterogeneous disorder. In < 5% of cases, a mutation in the AHJ1 gene can be detected. Considering the differential diagnosis, it is important to differentiate JS from other rare related syndromes which also include hypoplasia of the vermis, mental retardation, ataxia or ocular symptoms (Table).

JS was first described in 1969 by Marie Joubert. There are only few data regarding the prognosis and the outcome of affected patients so far. There is a wide range of developmental disability, which varies from children attending mainstream school to severely handicapped children. Speech difficulties, cognitive deficits and behavioural problems seem to be prominent. Hodgkins reported on 29 Patients, 5 of whom had died in early childhood. 18 patients could be followed, 12 of those learned walking between 22 months and 10 years of age. Of the 15 children older than 5 years, 11 obtained an intelligible speech, 6 attended mainstream school

(with a varying amount of help), 5 were moderately and 4 were severely handicapped. Concerning the renal and ocular symptoms it is known that these can progress in the course of the illness and that retinal involvement is often associated with renal cysts.

Genetic work-up of our patient (Prof. Boltshauser, Department of Neuropediatrics, University Children's Hospital of Zurich in collaboration with the laboratory of Prof. Valente, Rome) revealed a mutation of the CEP290 gene on chromosome 12. CEP290 mutations have previously been described in five families with variable neurological, retinal and renal manifestations (6). CEP290 encodes for a large protein of centrosomal and ciliary localization, thus linking Joubert syndrome to other human ciliopathies (6, 7).

ADDENDUM
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Table

	Joubert syndrome	Dandy Walker	Congenital Disorder of glycosilation	Coach
Breathing	episodic tachypnea/apnea	normal	normal	normal
MRI	vermis hypoplasia, brainstem malformation, MTS	vermis hypoplasia, hydrocephalus	olivoponto-cerebellar atrophy	vermis hypoplasia
Renal involvement	yes	yes	usually not	yes
Eye involvement	yes	yes	yes	yes
Ataxia	yes	yes	yes	yes

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