

Joubert Syndrome

History and Overview

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Outline of presentation

- Historical remarks – with hints to later insights
- Face
- Behavior
- Outcome studies
- Oromotor function
- Cognition
- Imaging
- Genetics



Familial agenesis of the cerebellar vermis

A syndrome of episodic hyperpnea, abnormal eye
movements, ataxia, and retardation

Marie Joubert, M.D., Jean-Jacques Eisenring, M.D.,
J. Preston Robb, M.D., and Frederick Andermann, M.D.

SOME TWO YEARS AGO we investigated a child with profound psychomotor retardation who had had an occipital meningoencephalocele removed at birth. Contrast studies were carried out which showed a large midline defect in the posterior fossa and absence of the vermis. At the time we disregarded the nurses' comments about the child's abnormal breathing. A year later, Dr. P. P. Demers referred this patient's baby brother to us because he was concerned about his abnormal breathing and retarded development. It was then found that a third and older child in this family was retarded, ataxic, and breathing abnormally. Finally we were able to trace yet another sibling who had died in fancy and who, at autopsy, proved to have agenesis of the vermis. This diagnosis was then confirmed in the two affected living children by contrast studies.

From this investigation there emerged a familial syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and mental retardation associated with a common malformation in the four affected siblings, agenesis of

the vermis. This syndrome has not previously been described in the literature.

The affected children will be presented in the order in which the abnormality was identified, which happens to be in reverse to the birth order (Fig. 1).

CASE REPORTS

Case 1. M. D., a 6-month-old French Canadian boy, was admitted to the Montreal Children's Hospital on Oct. 9, 1967, for evaluation of abnormal breathing and developmental retardation. He was the last of six children in his sibship, born after a normal pregnancy. Forceps were used during delivery. There was no history of trauma or anoxia at birth; however, his breathing, even at birth, was abnormally rapid. He smiled early. At the age of

From the Department of Neurology, Montreal Children's Hospital, and the Department of Neurology and Neurosurgery, McGill University

Read in part at the meeting of The American Academy of Neurology, Chicago, April 1968

Submitted for publication Dec. 20, 1968; accepted Jan. 9, 1969.

Dr. Andermann's address is Montreal Neurological Hospital, 3801 University Street, Montreal, Quebec, Canada.

Joubert, Eisenring,
Robb, Andermann
Neurology 1969



First description 1969 Joubert et al

- 4 affected siblings
- Variable clinical presentation and outcome
→ intrafamilial heterogeneity
- Parents: remotely related
- Family name: Duquette
- Previous index patient presented at 1998 meeting in Montreal
31 years old



**Second Report - Index Patient seen in
Zürich 1976
for abnormal respiratory pattern**



neuropädiatrie 8:57—66 (1977)

JOUBERT SYNDROME: EPISODIC HYPERPNEA, ABNORMAL EYE MOVEMENTS, RETARDATION AND ATAXIA, ASSOCIATED WITH DYSPLASIA OF THE CEREBELLAR VERMIS

E. Boltshauser and W. Isler

Department of Neurology, Children's University Hospital, Zürich

Boltshauser, E. and Isler, W.: Joubert syndrome: episodic hyperpnea, abnormal eye movements, retardation and ataxia, associated with dysplasia of the cerebellar vermis. Neuropädiatrie 8: 57—66 (1977). A unique syndrome consisting of episodic hyperpnea, abnormal eye movements, ataxia and mental retardation, associated with agenesis of the cerebellar vermis, has been delineated in four siblings by Joubert et al. (1969). We describe three other children with this clinically recognizable condition which we suggest to call Joubert syndrome.

There is good evidence that it is inherited as autosomal recessive. Two of our patients were brothers, the third child's parents were related. Recognition of this syndrome is important in view of prognosis and for genetic counseling.



Unexpected death of index patient at 23 months

Develop. Med. Child Neurol. 1978, **20**, 758–763

Uncommon Syndromes of Cerebellar Vermis Aplasia. I: Joubert Syndrome

R. L. Friede E. Boltshauser

SUMMARY

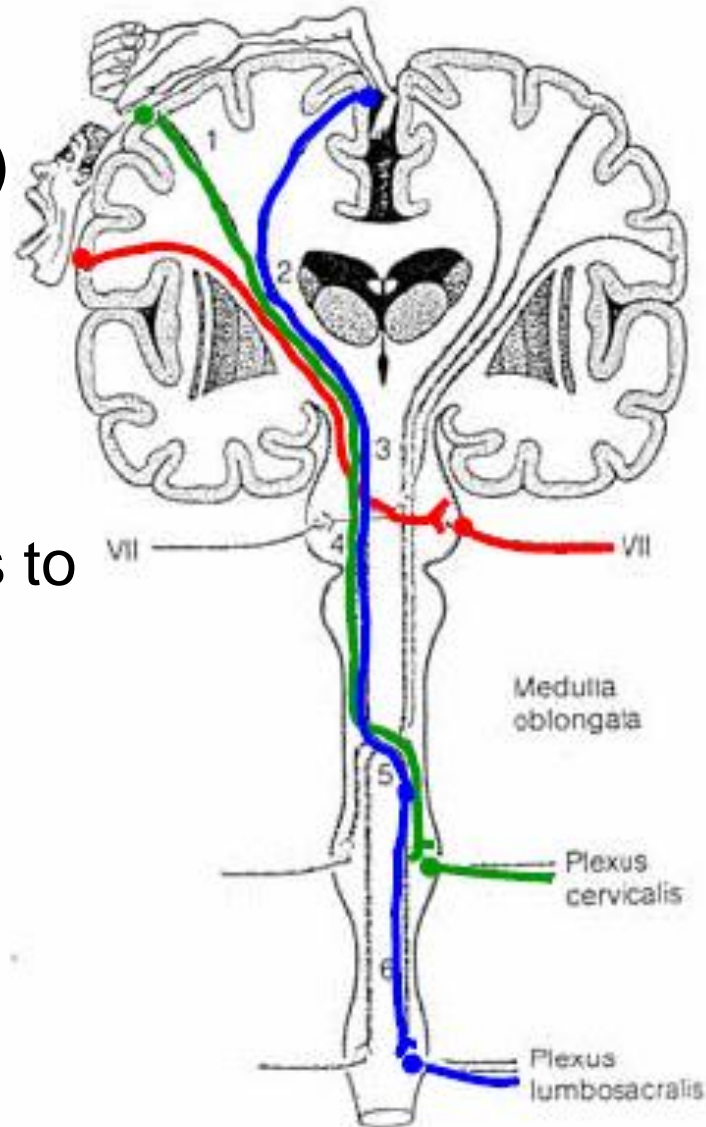
Necropsy findings are reported for a case of Joubert syndrome (familial aplasia of cerebellar vermis with episodic hyperpnea, abnormal eye-movements, ataxia and retardation). The findings consisted of an almost total aplasia of the cerebellar vermis; dysplasias and numerous heterotopias of cerebellar nuclei; **an almost total absence of pyramidal decussation**; and anomalies in the structure of the inferior olivary nuclei, the descending trigeminal tract, solitary fascicle and of the dorsal column nuclei. The lesion resembled the Dandy-Walker malformation or simple aplasia of the cerebellar vermis in some of its aspects, but there were numerous others to set it apart—at least tentatively—as a distinct nosologic entity.



Pyramidal tract - crossing at brainstem level

Neurons (pyramidal cells) in motor cortex

Descending axons cross to contralateral side



...almost complete absence of pyramidal decussation

- Finding later confirmed by Yachnis & Rorke (1999)
- Gene product of first detected gene (AHI1, 2004) mainly expressed in neurons of crossing axons of pyramidal tract and superior cerebellar peduncles
→ presentation by Dr. R. Ferland
- Tractography... (~2005 - ff)
confirmation → abnormal decussation of pyramidal tract (and tracts in superior cerebellar peduncles)



JOUBERT SYNDROME: CLINICAL AND POLYGRAPHIC OBSERVATIONS IN A FURTHER CASE

E. Boltshauser, M. Herdan, G. Dumermuth and W. Isler

Children's University Hospital, Steinwiesstr. 75, CH-8032 Zürich

(Received June 6, 1980; accepted July 2, 1980)

Boltshauser, E., Herdan, M., Dumermuth, G. and Isler, W.: Joubert syndrome: Clinical and polygraphic observations in a further case. Neuropediatrics 12: 181–191 (1981). To our knowledge, only 10 cases of *Joubert syndrome* have been published so far. In this paper, we describe the clinical, radiological (computerized tomography) and polygraphic findings in an additional patient. The female presented here is the product of consanguineous parents and a sibling of a previously reported infant. In addition to the well-known episodic tachypnea in an awake state, representing the clinical hallmark of this syndrome, this child also had bouts of tachypnea while asleep. Interestingly enough, these were confined only to non-REM sleep.

Cerebellar malformation dysplasia of cerebellar vermis mental retardation
respiration disorder apnea

- Sibling of index patient
- CT demonstration of abnormal vermis
- Intrafamilial heterogeneity
- 10 patients reported until 1981



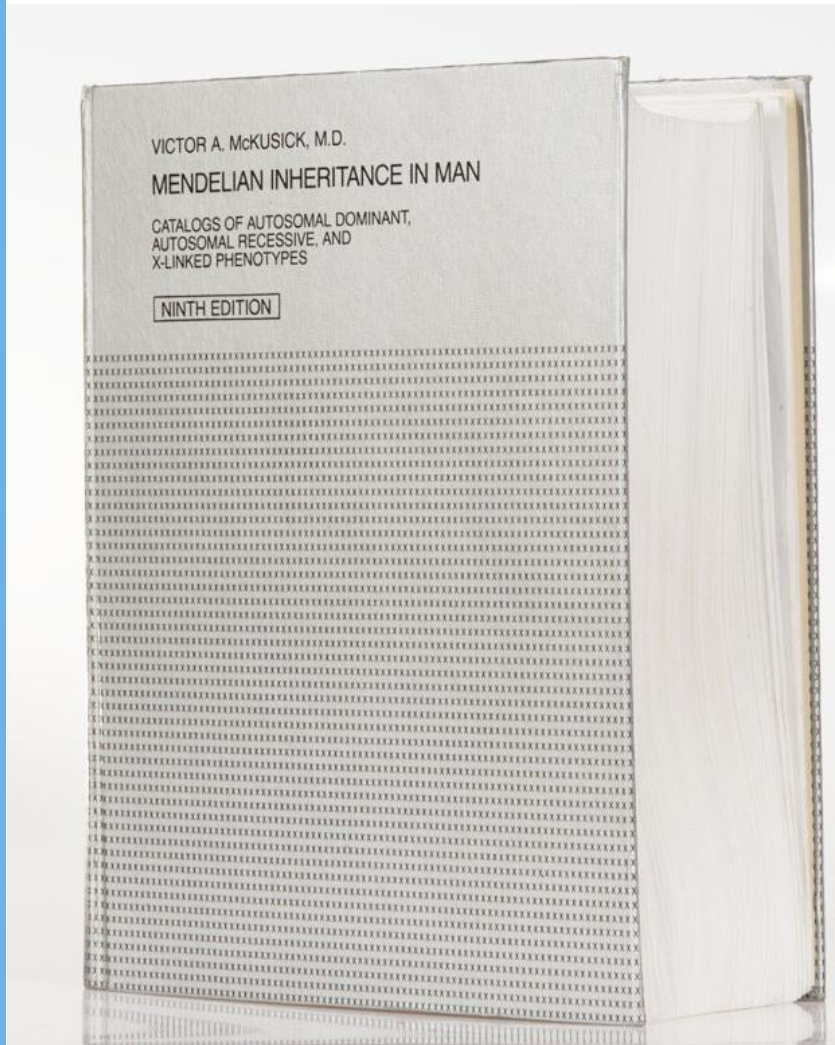
Information tools - then

- Publications (references) listed in print form in „Index Medicus“
assigned to key words (i.e. cerebellar disease)
→ search for article in library
- Victor McKusick:
Catalogue **M**endelian **I**nheritance in **M**en (**MIM**)
Printed editions...new edition every few years



Joubert Syndrome

1986 First entry in McKusick



*213300 CEREBELLOPARENCHYMAL DISORDER IV [CPD IV; CEREBELLAR VERMIS AGENESIS; JOUBERT SYNDROME; JOUBERT-BOLTSHAUSER SYNDROME]

De Haene (1955) collected from the literature 4 cases of total and 7 cases of partial agenesis of the vermis of the cerebellum, and added the only familial example: 3 brothers (1 autopsy) died at age 4-8 years, the illness being characterized by tremor and hypotonia. Joubert et al. (1969) described 4 French-Canadian sibs with this abnormality. By autopsy or pneumoencephalogram the vermis was shown to be completely or partially absent in all four. One also had an occipital meningocele. Symptoms included episodic hyperpnea, abnormal eye movements and psychomotor retardation. The oldest living sib was 8 years old. The parents were distantly related. See cerebellar hypoplasia (213000). Boltshauser and Isler (1977), who suggested the designation Joubert syndrome, described 3 cases, 2 of them sibs. Detailed neuropathologic findings on 1 of these were reported by Friede and Boltshauser (1978). Boltshauser et al. (1981) reported 2 affected sisters whose parents were consanguineous. Computed tomography is now the preferred way to demonstrate hypoplasia of the cerebellar vermis. Egger et al. (1982) described brother and sister (of Asiatic Indian extraction) with clinical features of the Joubert-Boltshauser syndrome (including tachypnea up to 95 respirations per minute) and by computed tomography hypoplasia of the vermis. One also had a cyst of the fourth ventricle. Both had postaxial polydactyly of the hands and feet and 1 had fleshy tumors of the tongue. Egger and Baraitser (1984) suggested that the sibs reported by Gustavson et al. (1971) and by Haumont and Pelc (1983) had the Joubert syndrome, not the Mohr syndrome (252100). Pierquin et al. (1989), however, concluded that the sibs reported by Egger et al. (1982) had a 'new' entity; see 220220. Lindhout et al. (1980) and Laverda et al. (1984) described associated chorioretinal coloboma (see 243910).

Boltshauser, E., Herdan, M., Dumermuth, G. and Isler, W.: Joubert syndrome: clinical and polygraphic observations in a further case. *Neuropediatrics* 12: 181-191, 1981.

Boltshauser, E. and Isler, W.: Joubert syndrome: episodic hyperpnea, abnormal eye movements, retardation and ataxia, associated with dysplasia of the cerebellar vermis. *Neuropediatrics* 8: 57-66, 1977.

De Haene, A.: Agénésie partielle du vermis du cervelet à caractère familial. *Acta Neurol. Belg.* 55: 622-628, 1955.



Information tools - now

- PubMed (U.S. National Library of Medicine and National Institute of Health)
- McKusick catalogue **Online** → **OMIM**
- Homepages of Institutes, Patient Organisations...



Diagnostic tools - then

■ Imaging

1971 prototype CT scanner (London)

1970-ies CT subsequently introduced into clinic

MRI in clinic introduced ~ 1983

→ **Non-invasive recognition of cerebellar vermis agenesis → modification of diagnostic criteria**

■ Genetics

1959 → 46 human chromosomes

~1990 first reports about mutated genes



1985 Visit E.B. to Baltimore ... with consequences

- Guest of Prof. Hugo Moser, Kennedy Krieger Institute
- Seminar on Joubert Syndrome
- Dr. Bernhard Maria in the audience
Child Neurology Fellow at Johns Hopkins
- Patient on ward diagnosed with JS !
Daughter of Cheryl Duquette

- 1992 Joubert Syndrome Foundation



Tribute to Dr. Bernhard Maria

- Professional advisor of JSF
- Initiated many research studies
- Molar Tooth Sign defined (1995)
- Spread knowledge about JS through conferences and publications
- Initiated satellite meeting on JS in Montreal 1998 to Child Neurology Society Meeting



Joubert Syndrome Foundation JSF

- 1992 founded

Co-Founders:

Ch.Duquette, J.A. Eastwood, M. Van Damme

- Services

- Newsletter
- Biannual conference
- International networking
- Support of research
Data for several studies acquired at conferences !
- „plays an important role in educationg physicians...“



Joubert Syndrome

Prevalence

World wide occurrence

- Prevalence (in U.S.)
estimated ~ 1:80'000
likely to be an underestimate
Orphan disease
(prevalence < 1:2'000 ; European definition)
- Reported from (alphabetical order, not complete)

Australia, Arab countries, Brazil, Canada, Europe,
India, Israel, Japan, Pakistan, Russia, Singapore,
Taiwan, Turkey, USA



Literature – a note of caution

Plenty of published **false** diagnoses in the field of cerebellar malformations including...

- Joubert syndrome
- Cerebellar hypoplasia
- Rhombencephalosynapsis
- Dandy-Walker Malformation
- etc



Joubert Syndrome – Published Misdiagnoses (Selection)

- **Van Royen-Kerkhof et al**
Coexistence of Gaucher disease type 1 and Joubert syndrome
J Med Genet 1998;35:965-966
- **Mittler et al**
Image of the month: Joubert syndrome
Pediatr Neurosurg 1999;30:218
- **Haug et al**
OFD II, OFD VI and Joubert syndrome manifestations in 2 sibs
Am J Med Genet 2000;91:135-137
- **Donkelaar et al**
A case of Joubert's syndrome with extensive malformations
Clin Neuropathol 2000;19:85-93
- **Natacci et al**
Patient with large 17p11.2 deletion presenting with Smith-Magenis syndrome and Joubert syndrome phenotype
Am J Med Genet 2000;95:467-472
- Etc



Respiratory pattern

- Recognised as special feature in first publications
- Episodes of tachypnea and apnea
- Important initial diagnostic feature
- Later experience: not consistent
- Pattern also seen in other syndromes

→ presentation by Dr. Maida Chen



Facial phenotype

- Macrocephaly (large head)
 - Prominent forehead
 - High-arched eyebrows
 - Epicanthic folds
 - Nose: anteverted nostrils
 - Low-set ears
 - Open mouth → triangular → rhomboid shape
 - Tongue often protruded
 - (Ptosis)
- Phenotype NOT consistent
- Change over time



Facial phenotype in adults

- Mouth closed
- Tongue may be enlarged
- Midface hypoplasia („flat“ midface)
- Prominent chin



Behavior

- Observations ...reports by parents
- Very few systematic studies
- Variability ! Spectrum !

- Sensitivity to noise
- Majority of children with JS „easy“ to handle
- Minority with behavioral difficulties
(hyperactivity, aggression, withdrawal, self-injury...)
- Not (classical) autism

- Situation in adults ???



Long - term outcome

- Few studies !

First studies published before genetic insight

Initial impression: JS confined to brain

- 1997 Steinlin, Boltshauser (Zürich) n=19
- 1998 Gitten, Maria n=17
- 2004 Hodgkins (GOS Hospital London) n=29

→ Early awareness on: retinopathy, ocular movements, tongue movements, cognitive function, kidney and liver involvement...

→ Presentations on Eye, Kidney, Liver disease by Drs. Weiss, Hildebrandt, Gunay-Aygün, Heller

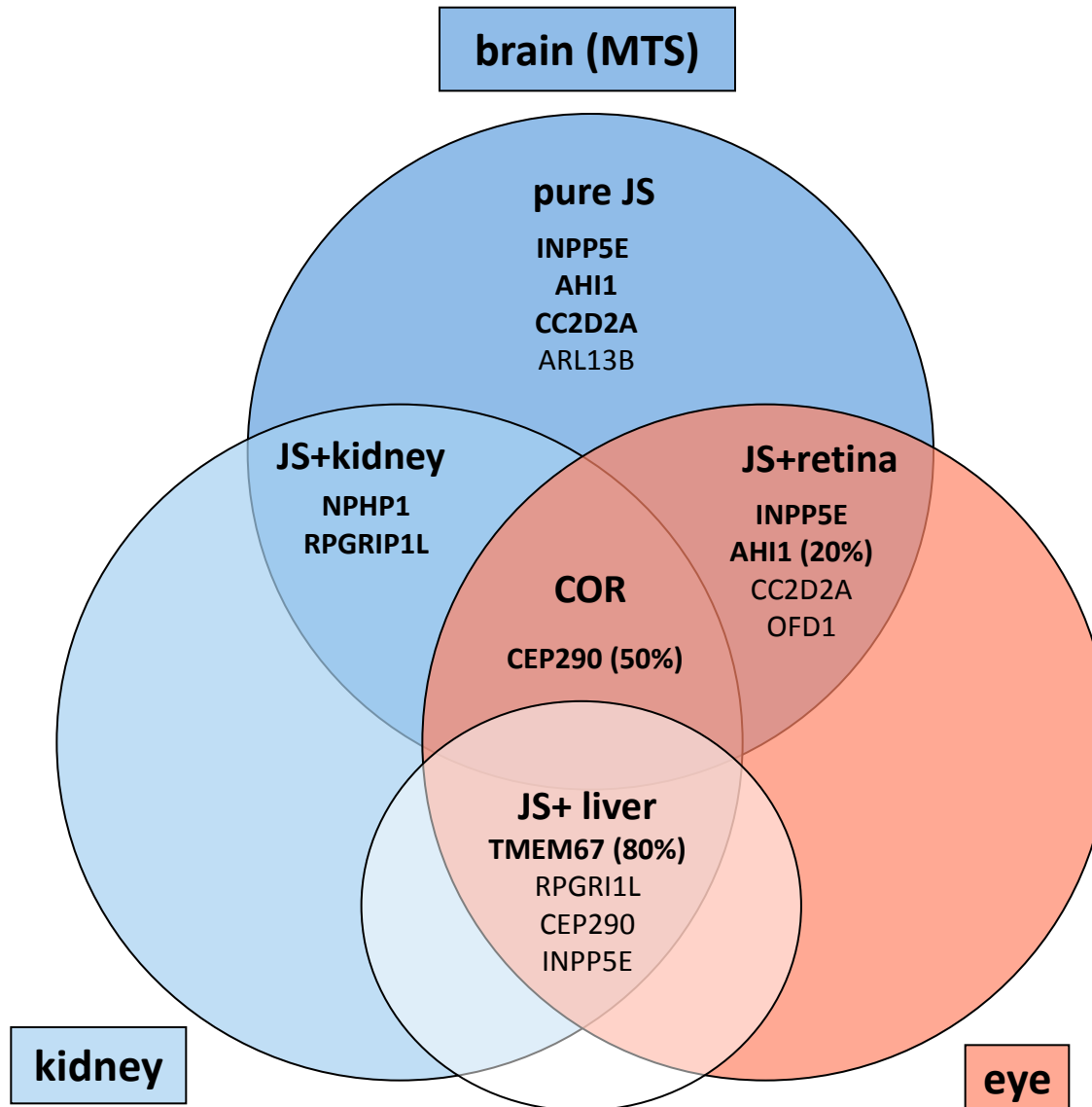


First outcome studies

- Variable clinical phenotypes
(additional findings as polydactyly, encephalocele...)
(intrafamilial variability !)
- Variable additional organ involvement
→ Joubert syndrome „goes beyond brain“
→ sub-types considered
- Phenotype – Genotype correlation ?
- → presentation by Dr. Dan Doherty



Genotype-phenotype correlates in JSRD



Courtesy Dr.E.M.Valente



Extra – facial phenotype inconsistent

- Occipital encephalocele
- Polydactyly
- Short stature
- Scoliosis (mainly in JBTS7 ?)
- Enoral abnormalities (confined to subtype OFD VI ?)

- Hoarse voice



Rarely reported features

(related ? coincidence ?)

- Hydrocephalus
- Congenital cataract
- Hirschsprung disease
- Epilepsy
- Situs inversus
- Cardiac malformation

Microcephaly is not a feature !



Oromotor function and communication

- Tongue initially often intermittently protruded
- Lateral tongue movements often limited
„Tongue apraxia“
impaired expressive speech, often mainly in vowels
- Verbal communication may be impaired
(may be mistaken as autistic element)
- Comprehension is better than expression
- Swallowing usually not impaired (exceptions)



Developmental delay

Assessment of abilities hindered by various impairments

- Muscle hypotonia
- Ataxia
- „Clumsiness“
- Tongue apraxia
- Oculomotor apraxia (eye movements)



Cognitive functions

Memo – early publications

„... retardation...“



Neuropediatrics 2009;40:287-290

Normal Cognitive Functions in Joubert Syndrome

Authors

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Affiliations

Affiliation addresses are listed at the end of the article

20 year old woman, MTS, Mutation in JBTS1 gene
Full scale IQ 94.
Two severely affected brothers



Neuroimaging

Memo:

increasing access to MRI only in late 80-ies, early 90-ies

previously – first reports:

demonstration of cerebellar pathology by (invasive)
pneumoencephalography



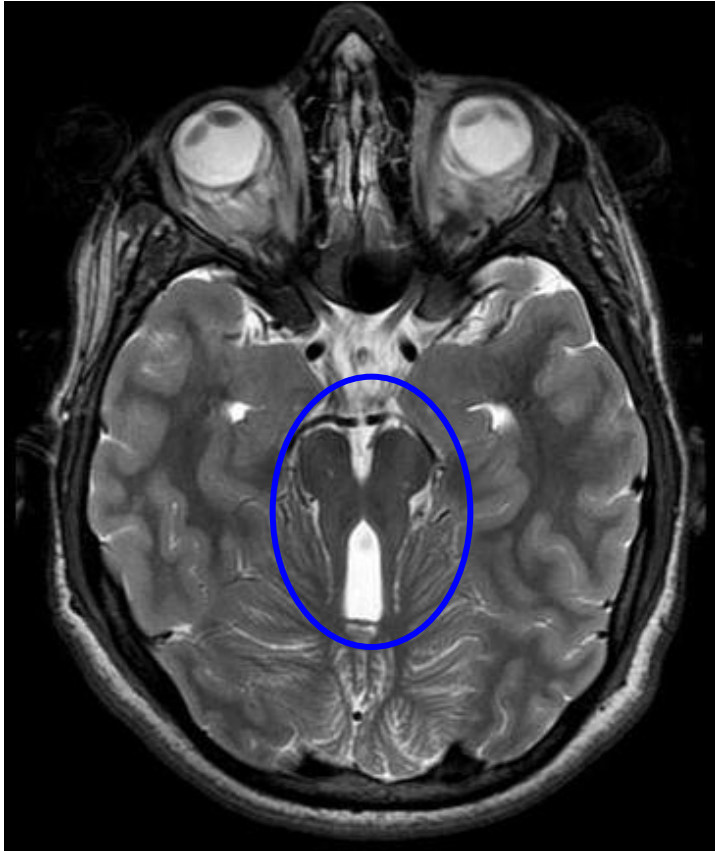
Molar Tooth Sign

Diagnostic ? – specific ?

- 1995 MTS defined by B.Maria & al
(Abstract 1995 Ann Neurol, full paper 1997 J Child N)
→ required for diagnosis
→ specific for JS
- 1997 MTS in OFD VI, Al-Gazali et al, J Med Genet
- 1999 Satran, Pierpont, Dobyns (MTS not limited to JS)
- 2004 Gleeson et al (MTS in multiple syndromes)



Molar tooth sign (MTS)



Molar Tooth Sign



Genetics

- Autosomal recessive inheritance suggested since first descriptions (affected siblings, related parents) (but: male preponderance in larger cohorts ?)
- 1980-ies: X-linked form with colobomas – not confirmed
- 1999: 1st gene locus chromosome 2 (Saar et al)
- 2002: 2nd gene locus (Keeler et al, Valente et al)
- 2004: 3rd gene locus on 6q23 (French-Swiss-Norw.)
- 2004: First gene on 6q23 (AHI1) identified
- 2011 (1st June) 12 genes published
- All genes related to function of primary cilia



Concept of ciliopathies

Genotype – phenotype correlation ?

- 2003 ff developed by Katsanis...Hildebrandt
- → presentation by Dr. F. Hildebrandt
- → presentation by Dr. D.Doherty



Joubert Syndrome - 40 years of learning...

Supported by

- New diagnostic tools
- Outcome studies – long-term observations
- Study of larger patients groups



Joubert Syndrome – special features

- Heterogeneity → clinical
 - genetic
 - neuroimaging
- Inter-familial and intra-familial variability
- Disorder of axonal guidance
- Disorder within spectrum of ciliopathies



Joubert Syndrome

...still many open questions

- New genes to be found
- Understanding pathogenesis
- Longterm studies
 - Organ involvement
 - Functional outcome
 - Quality of life
 -
- Therapeutic options ?



Acknowledgments

Thanks for teaching

- Patients and families
- Including Joubert Syndrome Foundation
- Colleagues

Thank you for inviting me to this conference

