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DIABETES INSIPIDUS



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DISCLOSURES

- Research Grants
  - Merck Serono, Pfizer
- Lecture Fees
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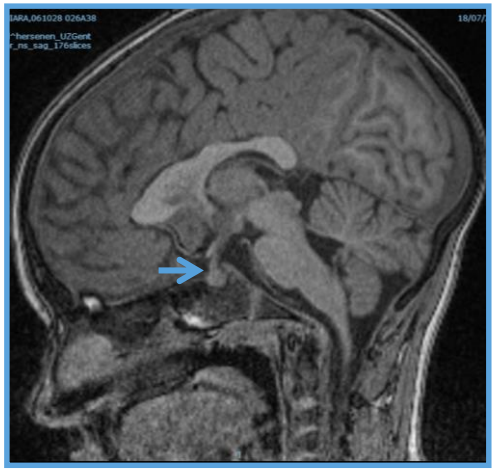
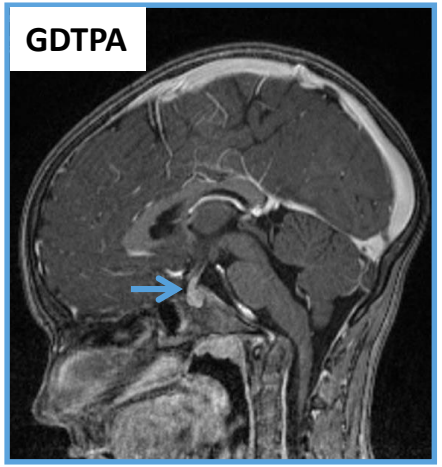
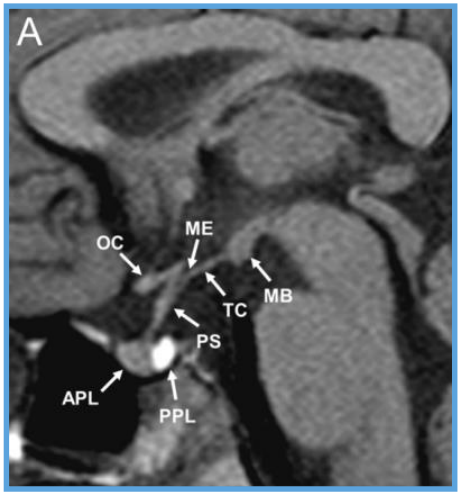
- Advisory Boards
  - Novo Nordisk, Sandoz, Merck Serono, Ascendis

CASE PRESENTATION

FEMALE, 8 YEARS OLD WITH POLYURIA AND POLYDIPSIA CENTRAL DIABETES INSIPIDUS AND THICK PS







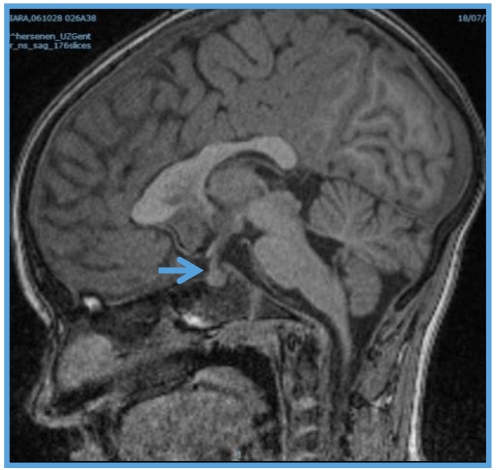
First MRI

1. **Absence of PPL hyperintensity**
2. **Uniformly thick PS**

APL, anterior pituitary lobe; GDTPA, gadolinium diethylenetriamine penta-acetic acid; MB, mammillary bodies; ME, median eminence; MRI, magnetic resonance imaging; OC, optic chiasm; PPL, posterior pituitary lobe; PS, pituitary stalk; TC, tuber cinereum

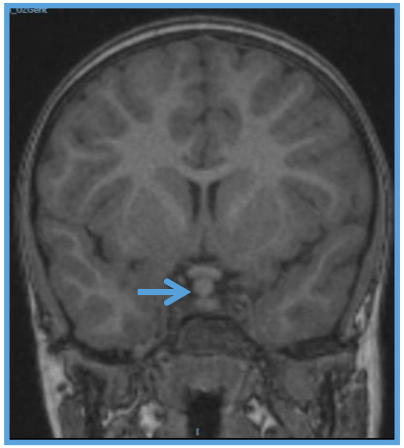
CASE PRESENTATION

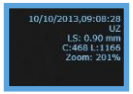
FEMALE, 8 YEARS OLD WITH POLYURIA AND POLYDIPSIA – GROWTH ARREST CENTRAL DIABETES INSIPIDUS AND THICK PS

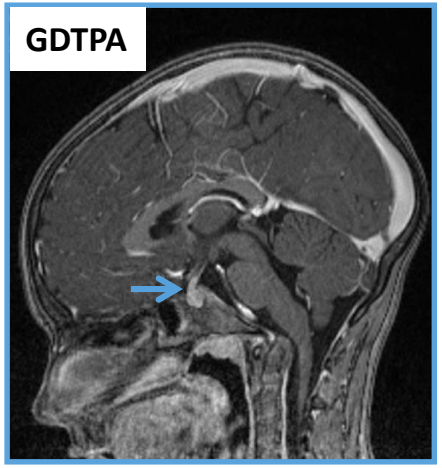


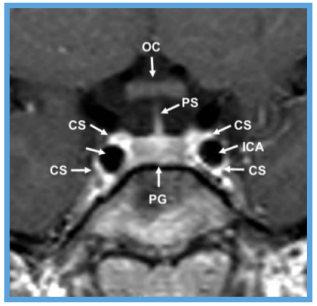
Second MRI – 3 months

1. Absence of PPL hyperintensity
2. Further thickening of PS









First MRI

1. Absence of PPL hyperintensity
2. Uniformly thick PS

CS, cavernous sinus; GDTPA, gadolinium diethylenetriamine penta-acetic acid; ICA, internal carotid artery; MRI, magnetic resonance imaging; OC, optic chiasm; PG, pituitary gland; PP, primary polydipsia; PS, pituitary stalk

CASE PRESENTATION

FEMALE, 8 YEARS OLD WITH POLYURIA AND POLYDIPSIA – GROWTH ARREST CENTRAL DIABETES INSIPIDUS AND THICK PS

- Central Diabetes Insipidus
- Growth deceleration
- Progressive pituitary stalk thickness

PS, pituitary stalk

CASE PRESENTATION

FEMALE, 8 YEARS OLD WITH POLYURIA AND POLYDIPSIA – GROWTH ARREST CENTRAL DIABETES INSIPIDUS AND THICK PS

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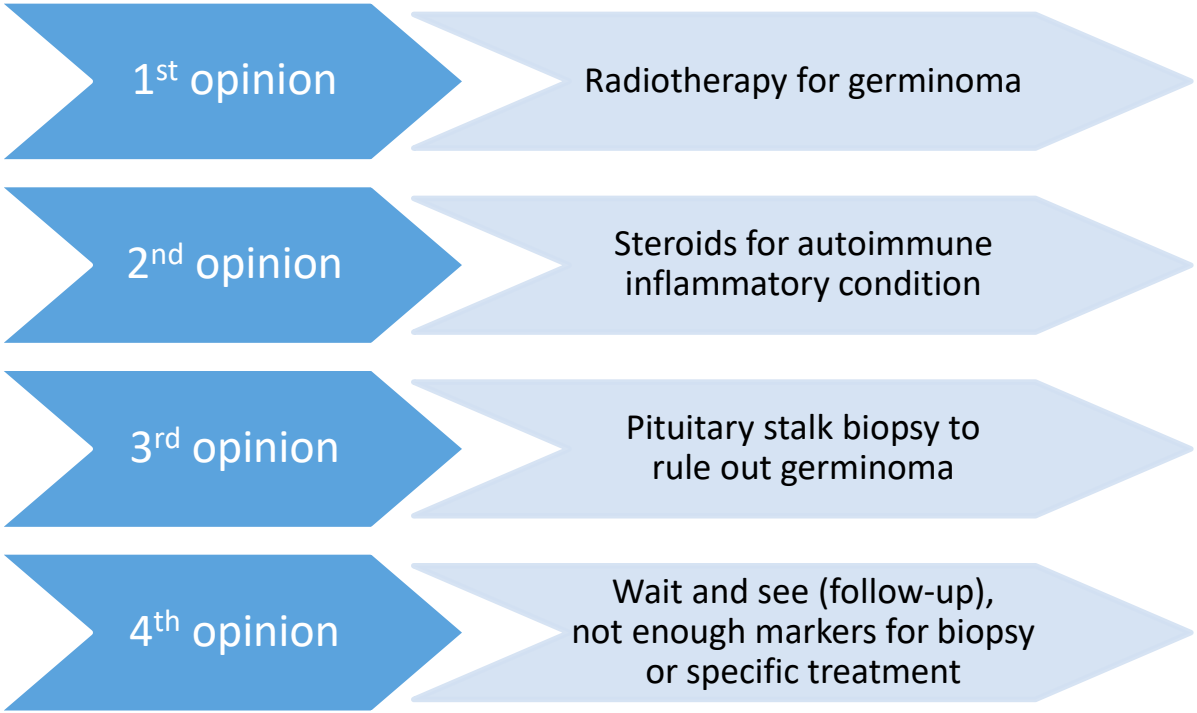
What is your suspected diagnosis?

1. Langerhans-cell histiocytosis
2. Lymphocytic – infundibulo – hypophysitis
3. Germinoma
4. Thick pituitary stalk of unknown origin
5. Something different

PS, pituitary stalk

CASE PRESENTATION
DIAGNOSTIC CHALLENGES



CDI AT TIME OF DIAGNOSIS CLINICAL PRESENTATION

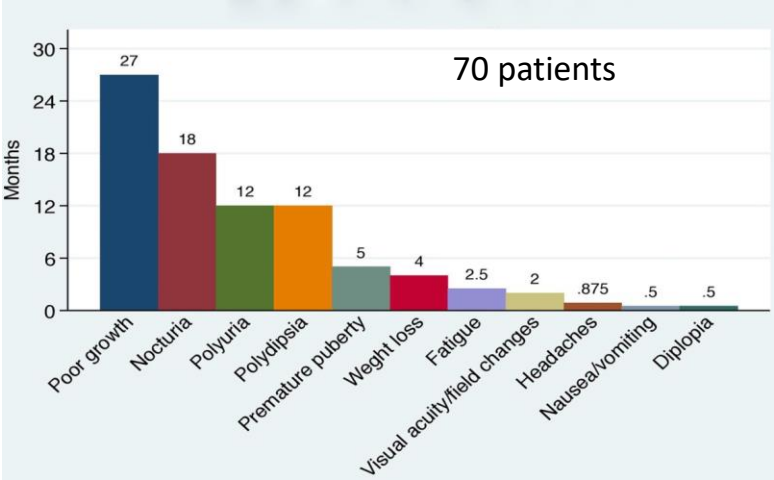


Figure 1 Median duration of symptoms / 70 patients with germ cell tumour.

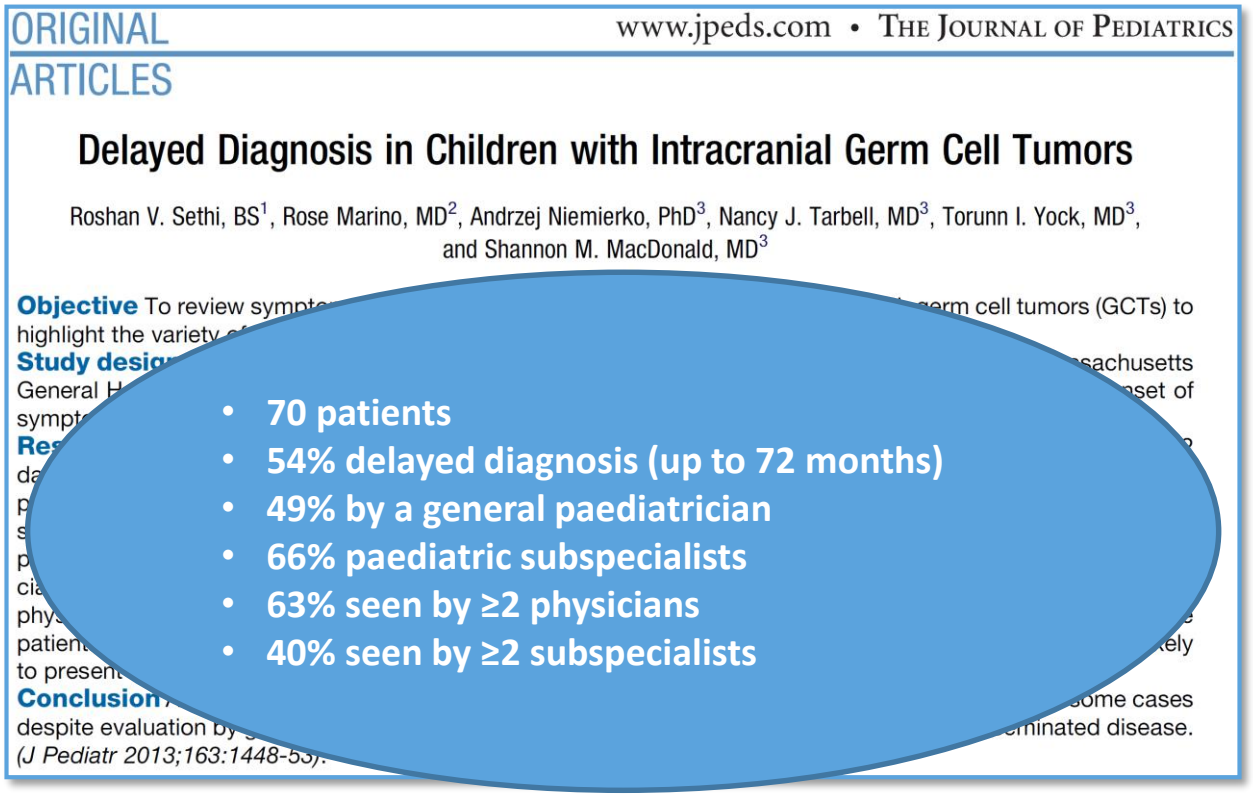
Roshan V. Sethi , Rose Marino , Andrzej Niemierko , Nancy J. Tarbell , Torunn I. Yock , Shannon M. MacDonald

The Journal of Pediatrics 2013

- 79 children and young adults with CDI[1]
- 40% of the 79 patients had symptoms other than polyuria and polydipsia at presentation
- Headache was not discriminatory
- Visual defect was associated with intracranial tumour
- We did not find that growth retardation was significantly more common in a single group of patients
  - This is in contrast with previous reports indicating that such delays strongly suggest an intracranial tumour as the cause of CDI

CDI, central diabetes insipidus

1. Maghnie M, et al. N Engl J Med. 2000;343:998-1007. 2. Sethi RV, et al. J Pediatr. 2013;163:1448-53



ORIGINAL ARTICLES

www.jpeds.com • The Journal of Pediatrics

Delayed Diagnosis in Children with Intracranial Germ Cell Tumors

Roshan V. Sethi, BS[1], Rose Marino, MD[2], Andrzej Niemierko, PhD[3], Nancy J. Tarbell, MD[3], Torunn I. Yock, MD[3], and Shannon M. MacDonald, MD[3]

Objective To review sympt… …germ cell tumors (GCTs) to highlight the variety …

Study desig… …sachusetts General H… …nset of sympt…

Res… da… p… s… p… cli… phys… patient… …kely to present…

Conclusion… …ome cases despite evaluation by … …minated disease.

(J Pediatr 2013;163:1448-53).

- 70 patients
- 54% delayed diagnosis (up to 72 months)
- 49% by a general paediatrician
- 66% paediatric subspecialists
- 63% seen by ≥2 physicians
- 40% seen by ≥2 subspecialists

Sethi RV, et al. J Pediatr. 2013;163:1448-53

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

MS, female, Caucasian with **increased thirst and polyuria** (diapers!) starting at 8 months (2 months after weaning)

- Pregnancy uneventful
  - normal delivery at term
  - birth weight 3600 gr
  - length birth 50 cm

Family history

- Unrelated Italian parents
- Grandfather with type-2 diabetes at the age of 69 years
- Grandmother with thyroiditis treated with L-Thyroxine since the age of 45 years

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

- Neonatal period unremarkable
- Normal psychomotor development for age
- Normal growth in the first 10 months
- Appetite reduction between 10-12 months with unsatisfactory weight gain
- Recurrent vomiting, constipation

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

- Clinical examination normal
- Kidney function normal
- Random serum sodium level 143-150 nmol/L
- Urine analysis normal

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

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What is your suspected diagnosis?

1. Idiopathic central diabetes insipidus
2. Nephrogenic diabetes insipidus
3. Primary polydipsia
4. Bartter's syndrome
5. Something different

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

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What would you like to do next?

1. Dehydration test
2. Measure AVP or copeptin
3. Endocrine evaluation
4. Brain MRI
5. Something different

AVP, arginine vasopressin; MRI, magnetic resonance imaging

CASE PRESENTATION
WATER DEPRIVATION TEST

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Time	9.00	10.00	11.30	12.30
Weight	10.200	10	9.840	9,805
Natremia	139	140	142	146
Plasma osmolality *Plasma AVP	289	291	294	298 *3,7pg/ml
Urine osmolality	74	187	245	405
Urine volume	335	245		180

*Normal value 2-5 pg/ml ; Posm= 2 [Na+] +[blood glucose/18]+ [urea/2.8 DDAVP test : UOsm = unchanged

AVP, arginine vasopressin; DDAVP, desmopressin; Posm, plasma osmolality; Uosm, urine osmolarity

INTERPRETATION OF FLUID DEPRIVATION AND DESMOPRESSIN TESTS IN POLYURIC PATIENTS

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Urine Osmolality (mOsmol/kg)		Diagnosis
After Fluid Deprivation	**After DDAVP**	
<300	>750	CDI
<300	<300	NDI
>750	>750	PP
300–750	**<750**	? Partial CDI ? Partial NDI ? PP

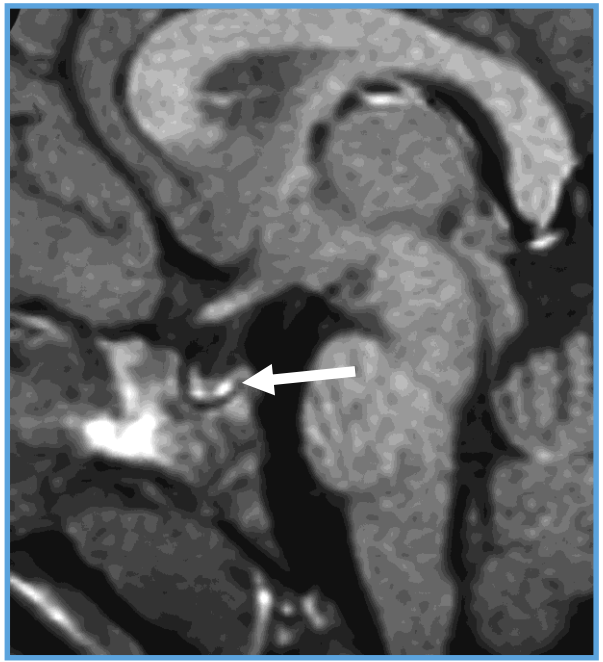
- The majority of children with Uosm of 600 or more at the time of normal serum osmolality do not have CDI or NDI
  - >50% increase of Uosm after DDAVP (CDI)
  - <50% increase of Uosm after DDAVP (NDI)

CDI, central diabetes insipidus; DDAVP, desmopressin; NDI, nephrogenic diabetes insipidus; PP, primary polydipsia; Uosm, urine osmolarity

Di Iorgi N, et al. Horm Res Paediatr. 2012;77:69-84

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

- No CNS malformations or abnormal signals
- Posterior pituitary hyperintensity
- Small anterior pituitary
- Normal pituitary stalk size and signal



CNS, central nervous system

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

- **Diagnosis of primary polydipsia**

- Reduction of daily fluid intake from 1/3 to 50%

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

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Would you like to do something else?

1. Clinical follow up
2. Endocrine follow up
3. Both 1 + 2
4. No follow up
5. Something different

CASE PRESENTATION
POLYURIA AND POLYDIPSIA

- Follow-up for one year
- Increased water demand
- Neurobehavioral change (irritable, aggressive)
- Poor growth
- Indications: psychologist

CASE PRESENTATION
SYMPTOMS-SIGNS AT THE AGE OF 2.2 YEARS

- Signs of dehydration
- Persistent thirst with limitation of fluid-intake
- Recurrent vomiting
- Constipation
- Irritability, aggressive
- Failure to thrive
- Growth retardation

CASE PRESENTATION
SYMPTOMS-SIGNS AT THE AGE OF 2.2 YEARS

- Serum sodium level 149 nmol/L
- UOsm= 79 mOsm/Kg/H2O
- Urinary volume after *ad libitum* fluid intake (2930 ml/day; weight 9.8Kg)
- DDAVP Challenge/Treatment: Reduction of fluid intake,
  UOsm > 500 mOsm/Kg/H_2O within 5 days

DDAVP, desmopressin; UOsm, urine osmolarity

CASE PRESENTATION
SYMPTOMS-SIGNS AT THE AGE OF 2.2 YEARS

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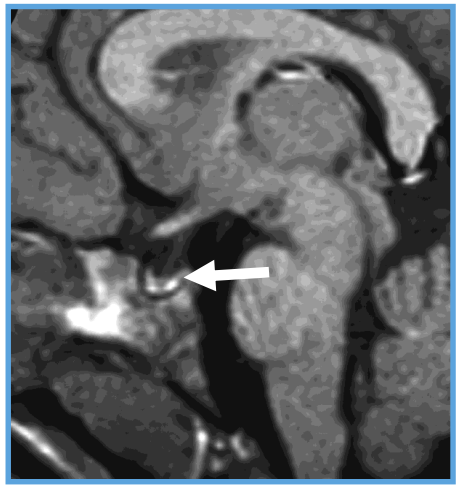
What would you like to do next?

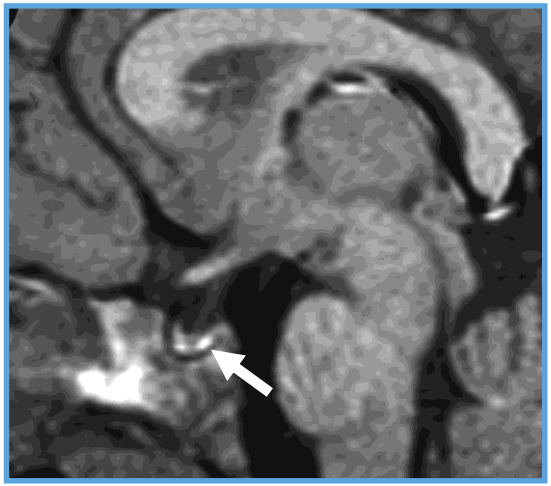
1. Start DDAVP
2. Endocrine re-evaluation
3. Measurement of AVP antibodies
4. Repeat Brain MRI
5. Something different

AVP, arginine vasopressin; DDAVP, desmopressin; MRI, magnetic resonance imaging

CASE PRESENTATION
CDI - SECOND BRAIN MRI

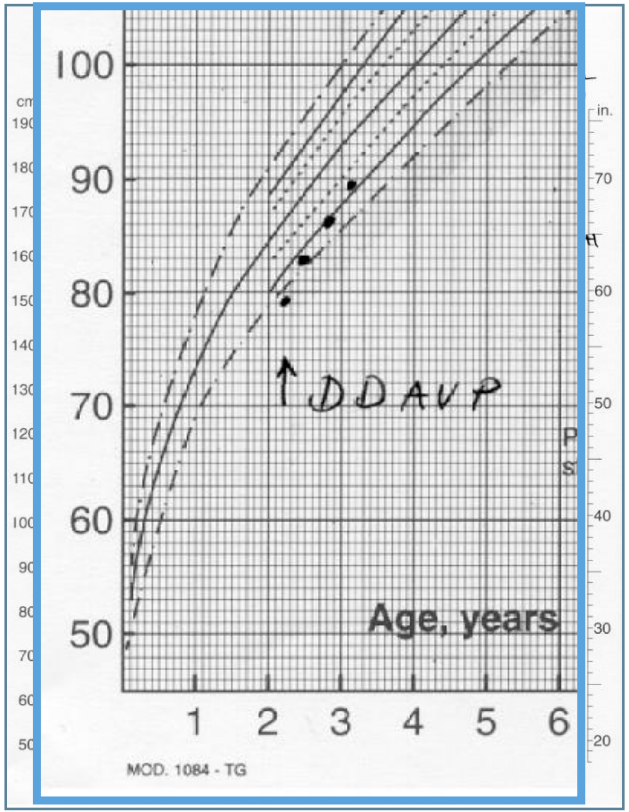
- No CNS malformations or abnormal signals
- Posterior pituitary hyperintensity
- Small anterior pituitary
- Normal pituitary stalk size and signal

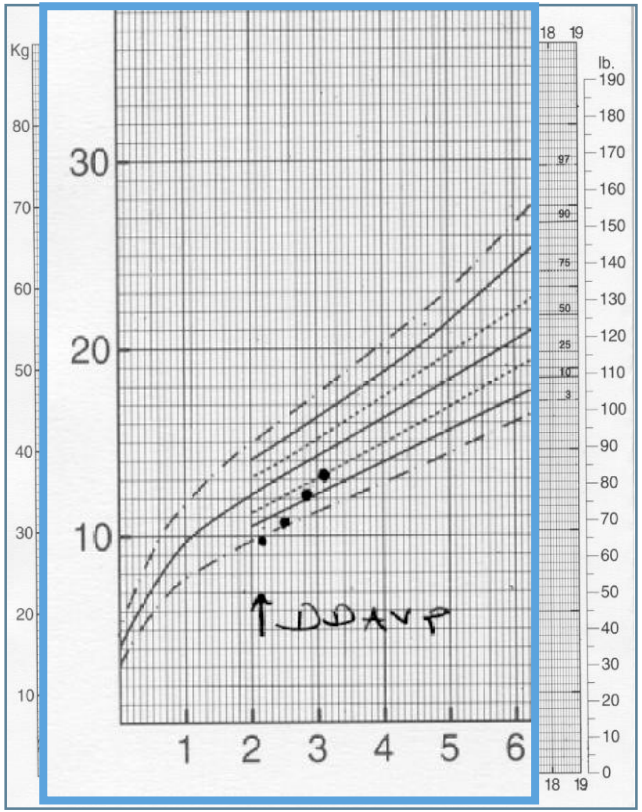




CDI, central diabetes insipidus; CNS, central nervous system; MRI, magnetic resonance imaging

CASE PRESENTATION
CDI AND GROWTH PATTERN





DIAGNOSIS OF CDI MISINTERPRETATION AND PITFALLS

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- Dehydration test and Partial CDI
  - Serum sodium 146 mEq/L
  - POsm 298 mOsm/kg
  - **UOsm 405 mOsm/kg**

- AVP measurement
  - **Plasma AVP** 3.7 pg/ml (nv 2-5)

AVP, arginine vasopressin; CDI, central diabetes insipidus; mEQ, milliequivalent; nv, normal value; POsm, plasma osmolality; UOsm, urine osmolarity

PITFALLS
AVP MEASUREMENT

- >90% of AVP in the circulation is **bound to platelets**, resulting in underestimation of amounts of AVP actually released
- **Incomplete removal of platelets** from plasma samples or **prolonged storage** of unprocessed blood samples can lead to falsely elevated and varying AVP levels
- Once secreted, AVP is **rapidly cleared** from the circulation
  - *In vivo* half-life of 24 min
- AVP is **unstable in isolated plasma**, even when stored at -20°C
- Because of its small size, AVP cannot **be measured by sandwich immunoassay**, but only by less sensitive competitive immunoassays

AVP, arginine vasopressin

DIAGNOSIS OF CDI MISINTERPRETATION AND PITFALLS

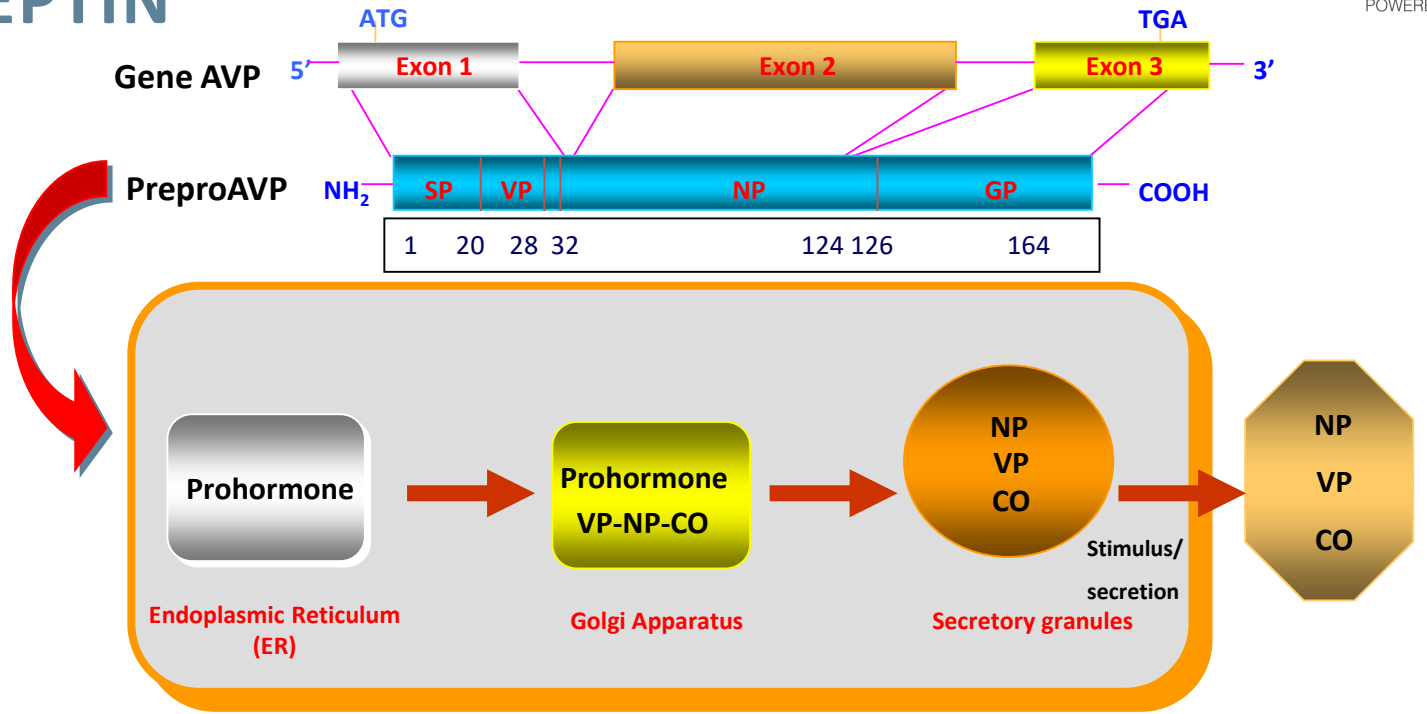
- Dehydration test and Partial CDI
  - Serum sodium 146 mEq/L
  - POsm 298 mOsm/kg
  - **UOsm 405 mOsm/kg**

- AVP measurement
  - Plasma AVP 3.7 pg/ml (nv 2-5)
  - **Copeptin**

AVP, arginine vasopressin; CDI, central diabetes insipidus; mEQ, milliequivalent; nv, normal value; POsm, plasma osmolality; UOsm, urine osmolarity

HUMAN PREPRO-8-ARGININE-VASOPRESSIN-NEUROPHYSIN II GENE

COPEPTIN

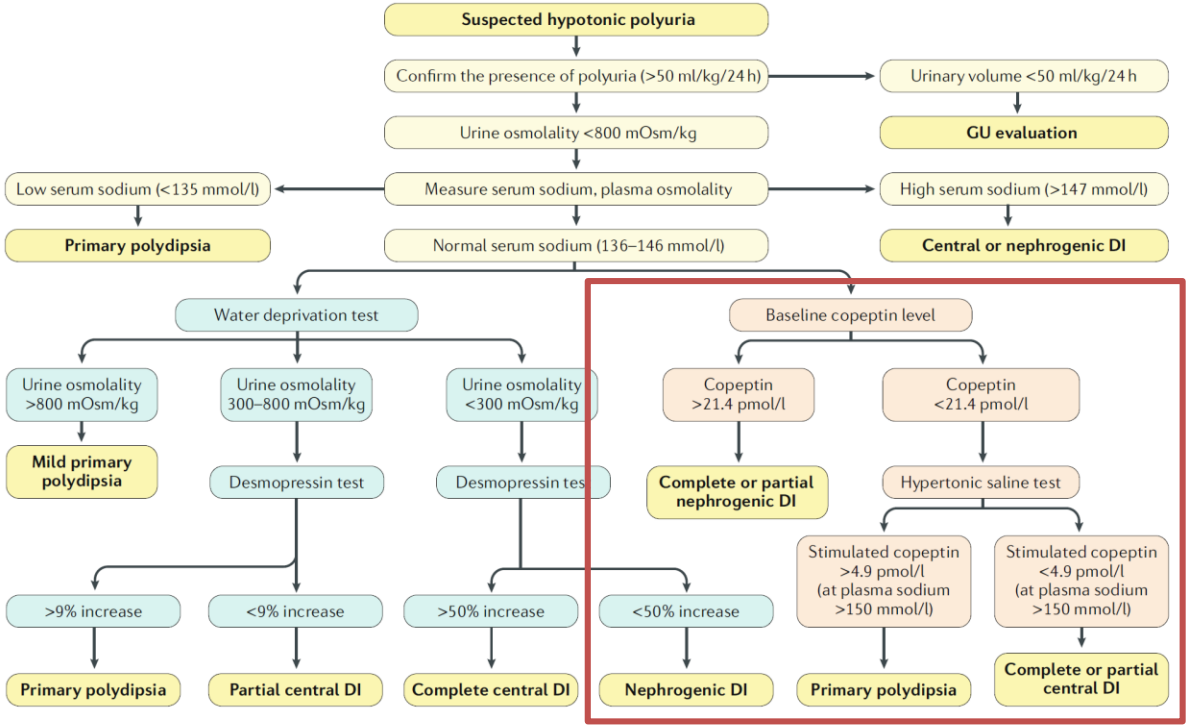


Cleavage of the prohormone generates AVP, neurophysin and the **C-terminal glycoprotein copeptin 39-amino acid-long peptide derived from the C-terminus of pre-pro-hormone of arginine vasopressin, neurophysin II and copeptin**

AVP, arginine vasopressin; ER, endoplasmic reticulum

Di Iorgi N, et al. Horm Res Paediatr. 2012;77:69-84

IS BASELINE/STIMULATED COPEPTIN RELIABLE IN THE DIAGNOSIS OF CENTRAL DIABETES INSIPIDUS?



DI, diabetes insipidus; GU, genitourinary

Christ-Crain M, et al. Nat Rev Dis Primers. 2019;5:54.

BIOCHEMICAL ASSESSMENT- DEPRIVATION TEST VERSUS COPEPTIN

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DIFFERENTIAL DIAGNOSIS OF CENTRAL/NEPHROGENIC DIABETES INSIPIDUS AND PRIMARY POLYDIPSIA

PRACTICE POINTS

- In patients with polyuria/polydipsia, baseline copeptin levels **>20 pmol/L** identify patients with **nephrogenic diabetes insipidus**
- Baseline copeptin levels **<2.6 pmol/L** identify patients with **complete central diabetes insipidus**
- Copeptin levels after **osmotic stimulation** ≤4.9 pmol/L can differentiate patients with partial central diabetes insipidus from patients with primary polydipsia (>4.9 pmol/L) with high sensitivities and specificities
  - An optimal accuracy of 93% was reached at a cutoff of 3,8 pM copeptin at 60' (sensitivity 93%, specificity 92%) during arginine stimulation test
- In **hyponatremia**:
  - **Low levels** of copeptin (<4 pmol/L) point to **primary polydipsia**
  - **High levels** of copeptin (>80 pmol/L) point to **hypovolemic hyponatremia**
- In other aetiologies of hyponatremia, copeptin levels overlap widely, thereby limiting its use in the differential diagnosis

1. Fenske W, et al. J Clin Endocrinol Metab. 2011;96:1506-15. 2. Fenske W, et al. N Engl J Med. 2018;379(5):428-39. 3. Winzeler B, et al. Lancet. 2019;394:587-95

DIAGNOSIS OF CDI MISINTERPRETATION AND PITFALLS

- Dehydration test and Partial CDI
  - Serum Sodium 146 mEq/L
  - POsm 298 mOsm/kg
  - UOsm 405 mOsm/kg
- AVP measurement
  - Plasma AVP 3.7 pg/ml (nv 2-5)
  - Copeptin
- MRI interpretation
  - Posterior pituitary hyperintensity – Anatomy vs function

AVP, arginine vasopressin; CDI, central diabetes insipidus; mEQ, milliequivalent; nv, normal value; POsm, plasma osmolality; UOsm, urine osmolarity

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Correlation between Magnetic Resonance Imaging of Posterior Pituitary and Neurohypophyseal Function in Children with Diabetes Insipidus

MOHAMAD MAGHNIE, ANDREA VILLA, MAURIZIO ARICO, DANIELA LARIZZA, STEFANO PEZZOTTA, GIAMPIERO BELUFFI, EUGENIO GENOVESE, AND FRANCESCA SEVERI

The basic defect underlying autosomal dominant DI is still unclear. A familial tendency toward dysgenesis or degeneration of the supraoptic-paraventricular nuclei has been suggested on the basis of autopsy findings (32–34). Recently, molecular analysis suggested that a defective AVP-prevasopressin-neurophysin-II-glycoprotein gene (35, 36) may result in autosomal dominant DI (37). Autosomal recessive DI in rats resulted from a single nucleotide deletion in the neurophysin gene (38). Two of our children with autosomal dominant DI unexpectedly had a normal bright signal, no hypothalamic lesion, and undetectable plasma AVP (39). This suggests that, at least in some cases, children with autosomal dominant DI are able to synthesize and store some amount of AVP in the posterior pituitary, but not necessarily to release it normally.

We concluded that the absence of a MR posterior pituitary signal in patients with DI is always associated with hypothalamic-neurohypophyseal axis lesion and correlates closely with undetectable plasma AVP. On the contrary, evidence of posterior pituitary hyperintensity does not rule out diagnosis of central DI, as release of stored AVP may be impaired in some cases of autosomal dominant DI as well as in some idiopathic forms. Isolated

AVP, arginine vasopressin; DI, diabetes insipidus; MR, magnetic resonance

Maghnie M, et al. J Clin Endocrinol Metab. 1992;74:795-800

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Familial neurohypophyseal diabetes insipidus in 13 kindreds and 2 novel mutations in the vasopressin gene

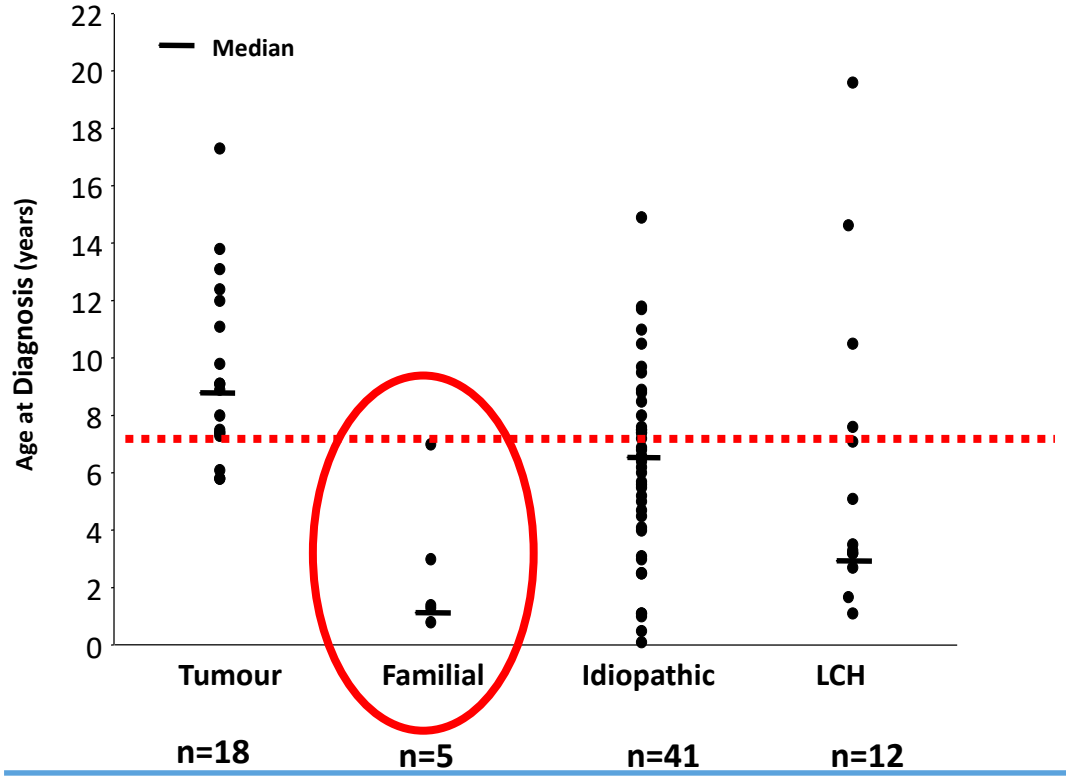
Giuseppa Patti[1,*], Saverio Scianguetta[2,*], Domenico Roberti[2], Alberto Di Mascio[3], Antonio Balsamo[4], Milena Brugnara[5], Marco Cappa[6], Maddalena Casale[2], Paolo Cavarzere[5], Sarah Cipriani[7], Sabrina Corbetta[8], Rossella Gaudino[5], Lorenzo Iughetti[9], Lucia Martini[5], Flavia Napoli[1], Alessandro Peri[7], Maria Carolina Salerno[10], Roberto Salerno[11], Elena Passeri[8], Mohamad Maghnie[1], Silverio Perrotta[2] and **Natascia Di Iorgi[1]**

Brain magnetic resonance imaging (MRI) revealed:

- Absence of posterior pituitary hyperintensity in 8 out of 15 patients
- Hypointense signal in 4 patients
- Normal signal in 2 patients

Patti G, et al. Eur J Endocrinol. 2019. pii: EJE-19-0299

AGE AT DIAGNOSIS ACCORDING TO THE CAUSE OF CENTRAL DIABETES INSIPIDUS



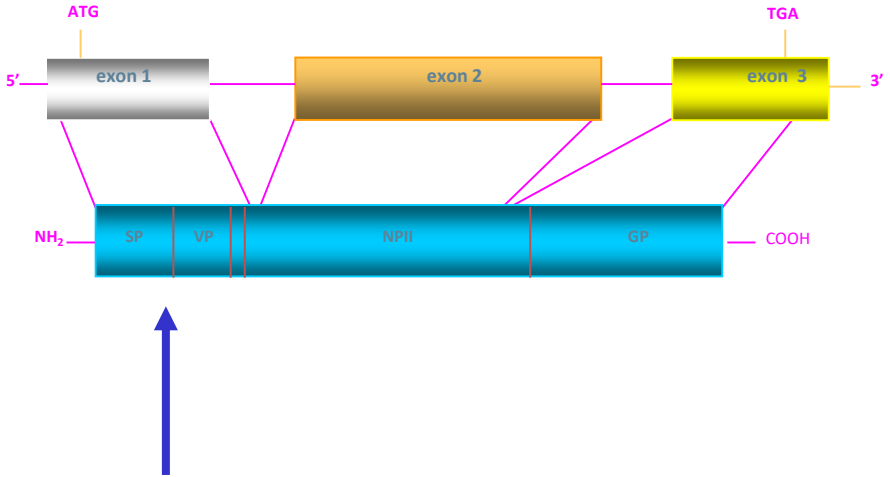
Patients who did not have an intracranial tumour were significantly younger at diagnosis than those who did (P<0.001 for all comparisons).

The horizontal lines indicate the medians.

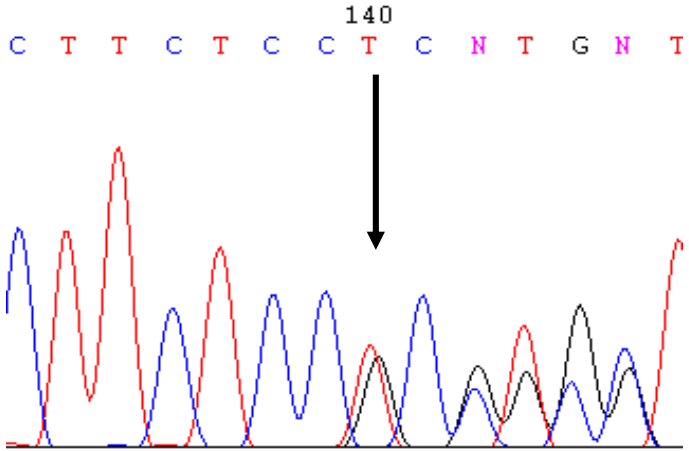
LCH, Langerhans cell histiocytosis

Maghnie M, et al. N Engl J Med. 2000;343:998-1007

AUTOSOMAL DOMINANT FNDI DE NOVO MUTATION AVP-NPII



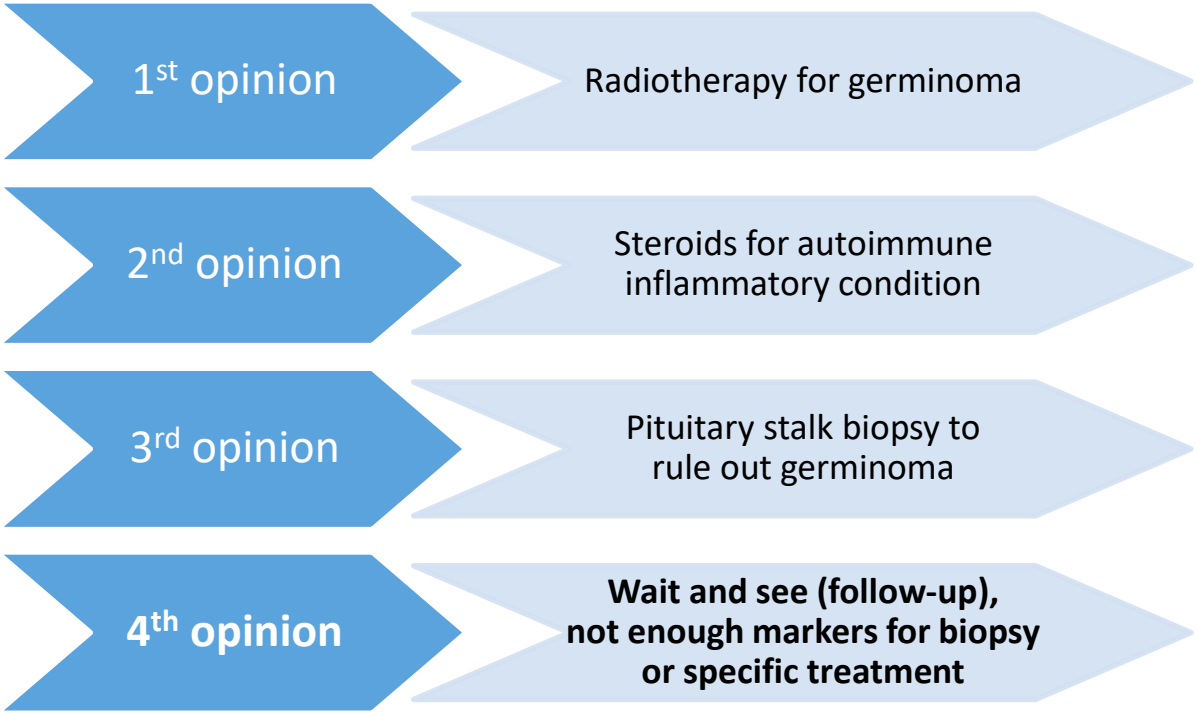
SP-S18del



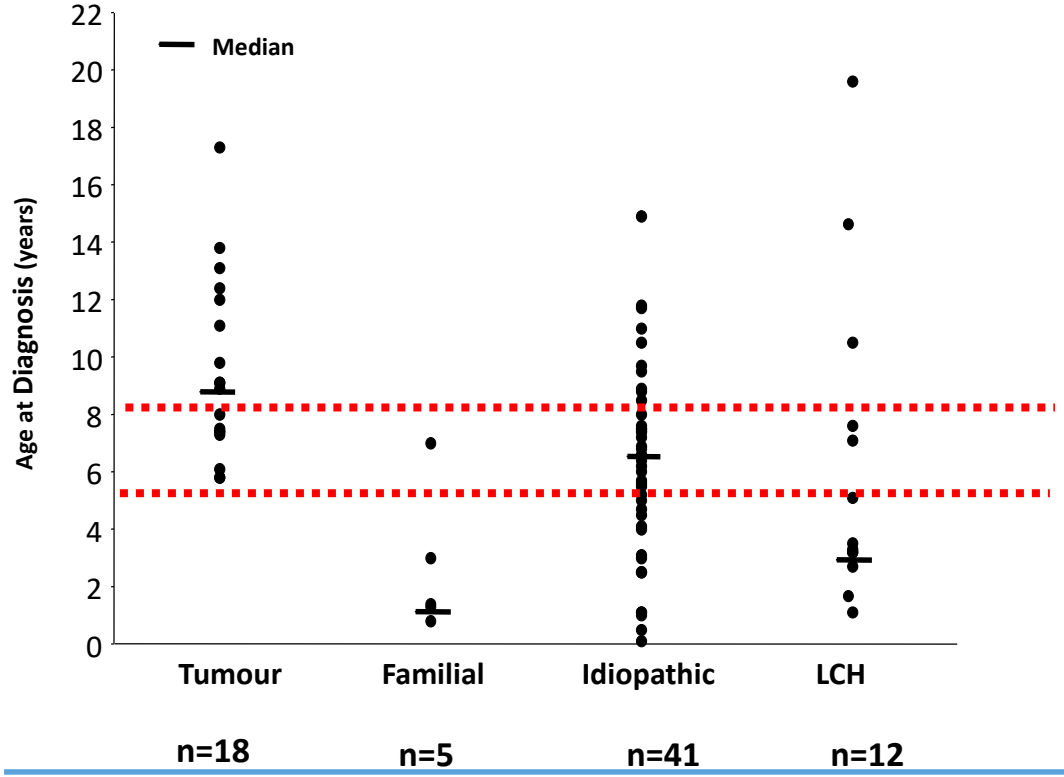
delTCC 52-54 SP-S18del

AVP-NPII, arginine vasopressin-neurophysin II; FNDI, familial neurohypophyseal diabetes insipidus

CASE PRESENTATION
DIAGNOSTIC CHALLENGES



AGE AT DIAGNOSIS ACCORDING TO THE CAUSE OF CENTRAL DIABETES INSIPIDUS



Patients who did not have an intracranial tumour were significantly younger at diagnosis than those who did (P<0.001 for all comparisons).

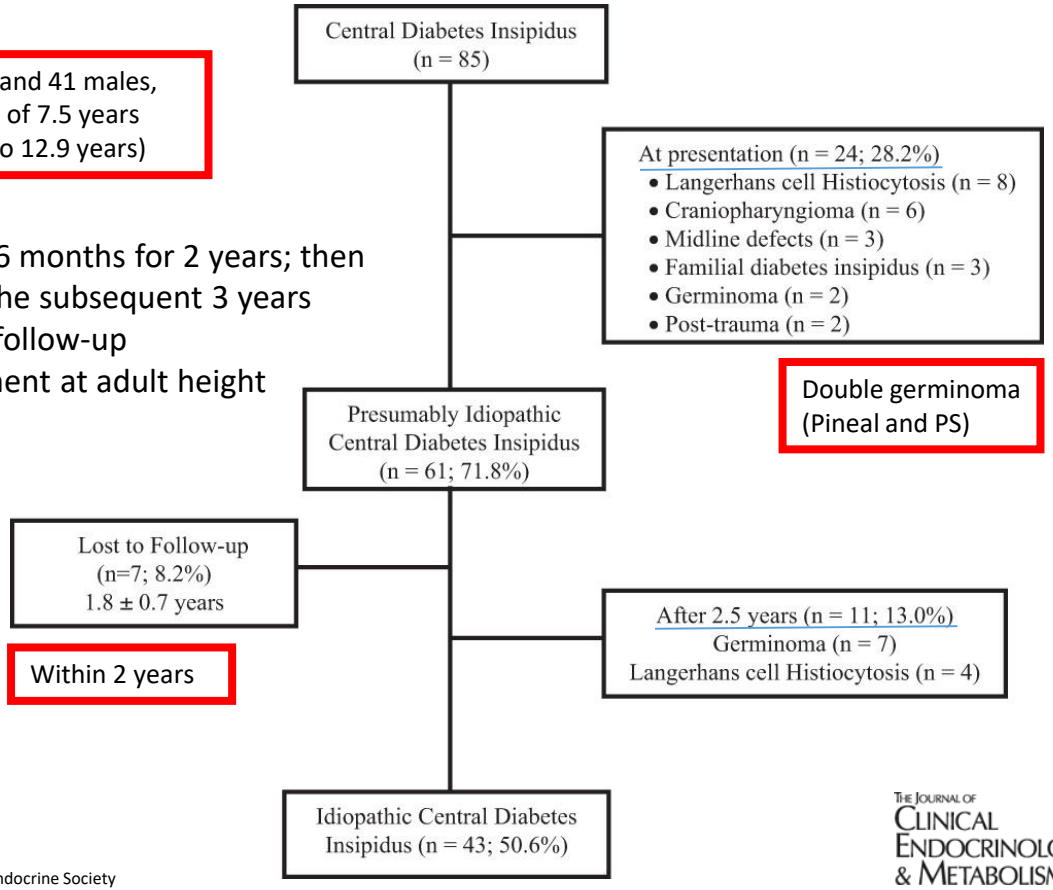
The horizontal lines indicate the medians.

LCH, Langerhans cell histiocytosis

Maghnie M, et al. N Engl J Med. 2000;343:998-1007

44 females and 41 males,
median age of 7.5 years
(range 1.0 to 12.9 years)

1998-2006
MRI every 6 months for 2 years; then yearly for the subsequent 3 years
Endocrine follow-up
Re-assessment at adult height



Double germinoma
(Pineal and PS)

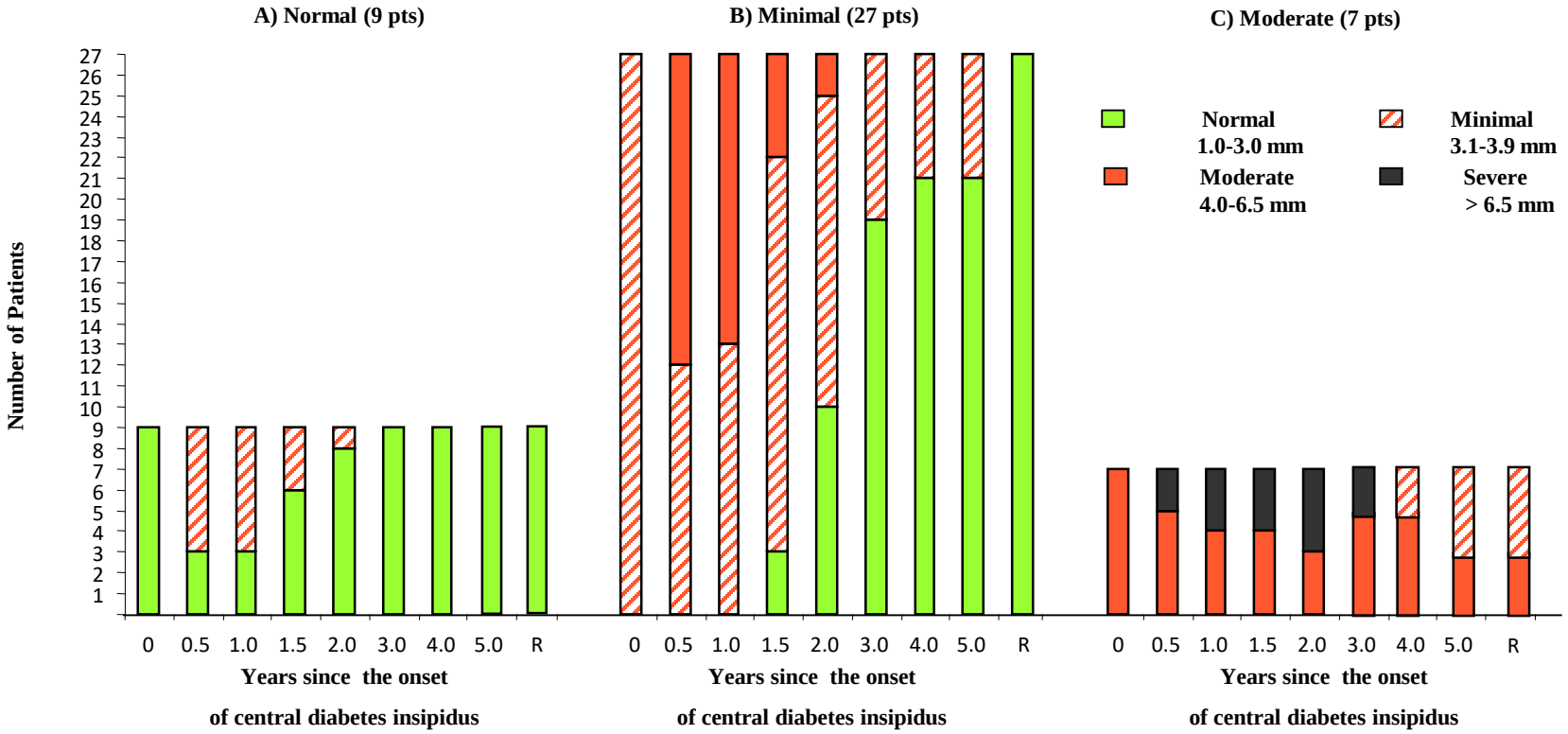
Within 2 years

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

PS, pituitary stalk

Di Iorgi N, et al. J Clin Endocrinol Metab. 2014;99:1264-72

PITUITARY STALK THICKNESS AT DIAGNOSIS



Pts, patients; R, reassessment

Di Iorgi N, et al. J Clin Endocrinol Metab. 2014;99:1264-72

FREQUENCY OF ANTERIOR PITUITARY HORMONE DEFECTS DURING FOLLOW-UP

PE connect® POWERED BY COR2ED

Based on pituitary stalk size at diagnosis of idiopathic central diabetes insipidus

Hormone defect	Pituitary stalk thickness (mm)*			Total	P
Type	Normal N=9	Minimal N=27	Moderate N=7	N=43	
GH – no. (%)†	5 (56)	23 (85)	7 (100)	35 (81)	0.05
TSH – no. (%)	0	16 (59)	7 (100)	23 (53)	<0.001
ACTH – no. (%)	0	3 (11)	6 (86)	9 (21)	<0.001
LH, FSH – no. (%)	0	5 (18)	7 (100)	12 (28)	<0.001

*Normal, between 1.0 and 3.0 mm; minimal enlargement, between 3.1 and 3.9 mm; and moderate enlargement, between 4.0 and 6.5 mm.
†All patients (n=35) with at least one hormone defect during follow-up have a growth hormone defect.

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone

Di Iorgi N, et al. J Clin Endocrinol Metab. 2014;99:1264-72

LONG-TERM COMPLICATIONS IN PATIENTS WITH A DIAGNOSIS OF IDIOPATHIC CDI

PE connect® POWERED BY COR2ED

3 patients
Langerhans-cell histiocytosis
(1 Bone, 2 Pulmonary)

up to 10 years after CDI diagnosis
1 scheduled for lung transplantation
1 died from lung complications

1 patient
Hodgkin's lymphoma

13 years after CDI diagnosis

Case 1

- A 12.5-year-old female with minimal pituitary stalk thickness developed a moderate enlargement of pituitary stalk during follow-up
- At the age of 21 she presented chronic long-lasting cough and progressive dyspnoea that were underestimated
- Chest computed tomography scans showed multiple cysts and computed tomography-guided biopsy was compatible with LCH
- The patient has been scheduled for lung transplantation

Case 2

- An 8-year-old female with moderate enlargement of the pituitary stalk developed GH and TSH defects within 2 years
- Ten years after the onset of CDI she developed back pain whose aetiology remained unidentified for 2 years
- Standard radiographs revealed lesions in the proximal right femur and L5 vertebral body; femur biopsy led to the diagnosis of LCH
- Five years after LCH diagnosis she is well without active disease

Case 3

- A 10- year old female with persistently moderate thickness of the pituitary stalk developed GH, TSH and adrenal deficiencies
- Nine years after the diagnosis of CDI, she presented with chronic cough
- Chest X-Ray and computed tomography scans were suggestive for pulmonary LCH that was confirmed by computed tomography-guided biopsy
- The disease was rapidly progressive and she died within 1.5 year

CDI, central diabetes insipidus; GH, growth hormone; LCH, Langerhans cell histiocytosis; TSH, thyroid-stimulating hormone

Di Iorgi N, et al. J Clin Endocrinol Metab. 2014;99:1264-72

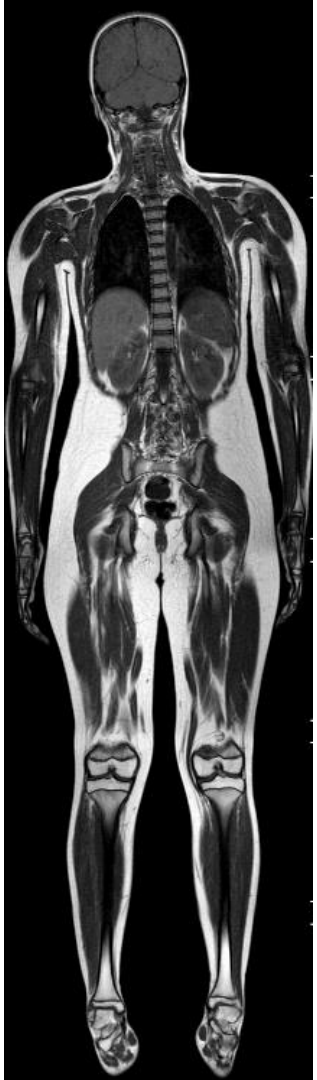
HOW DO I...

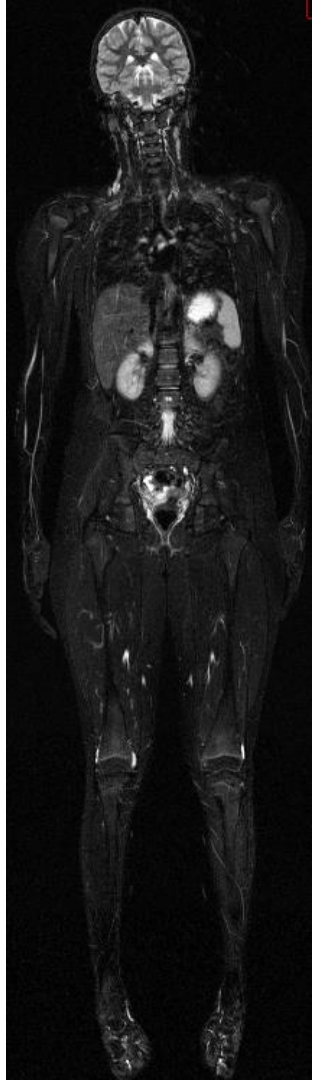
MANAGE A CHILD WITH CDI AND NORMAL PITUITARY STALK SIZE OR WITH A THICKENED PITUITARY STALK

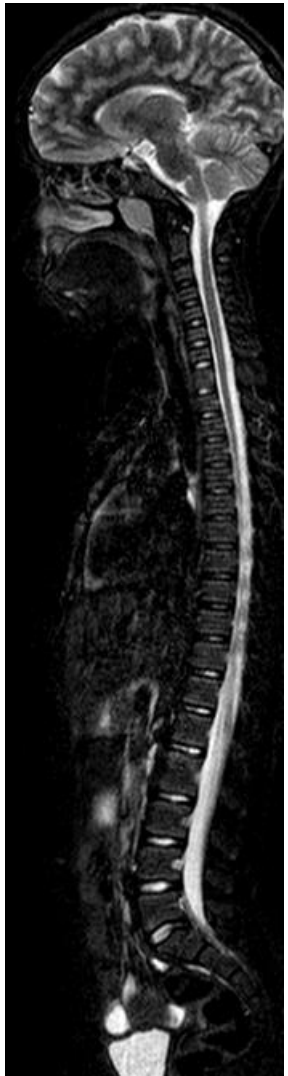
1. What is the contribution of whole-body MRI STIR to the diagnosis of patients with thickened pituitary stalk?
2. Role of T2-DRIVE MRI
3. When to perform a PS biopsy?

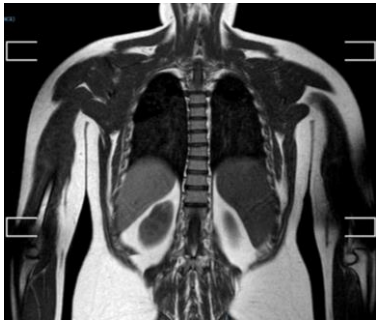
CDI, central diabetes insipidus; DRIVE, driven equilibrium; MRI, magnetic resonance imaging; PS, pituitary stalk; STIR, short tau inversion recovery

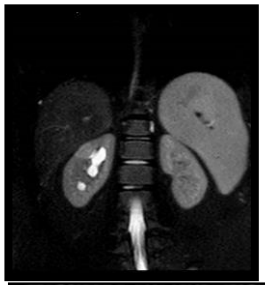
5/2016, Total body MRI- STIR sequence

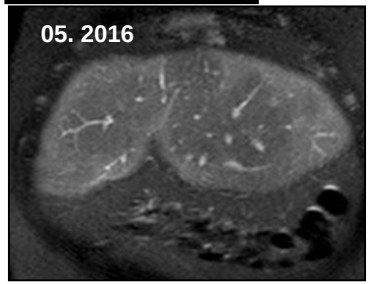






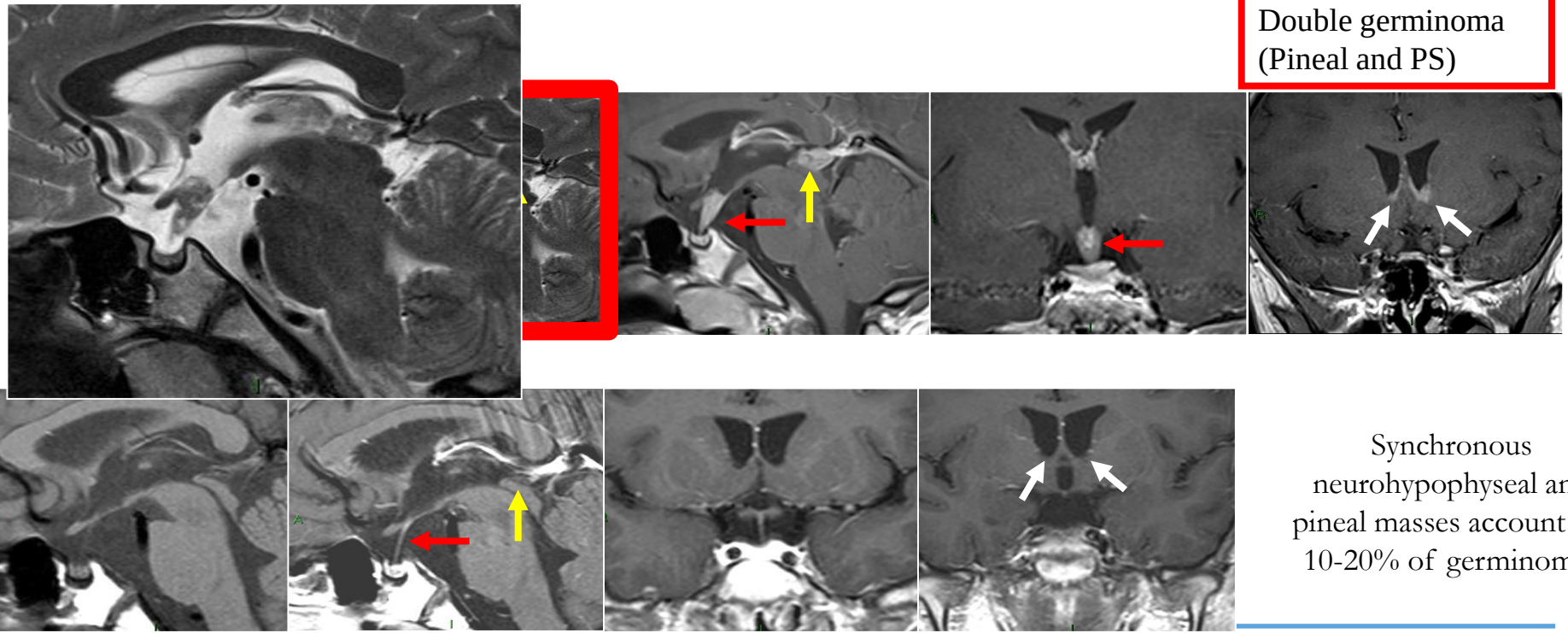






Signal abnormalities chest, liver, kidney (Superior polar)
Langerhans cell histiocytosis

DIAGNOSTIC WORK-UP
T2 DRIVE



Double germinoma
(Pineal and PS)

Synchronous neurohypophyseal and pineal masses account for 10-20% of germinomas

PITUITARY STALK BIOPSY CRITERIA

Author	Year	PST+CSF hCG	PST	PST	AP Size/other
Mootha	1997	+	Increase		
Leger	1999	+	Increase	7 mm	
Maghnie	2000 2003 2015	+ /–	Increase	> 6.5 mm	Increase/Third ventricle Brain stem/ Pons/ Cerebellum/White matter
Al-Agha	2001	+	Increase		
Alter	2002	+	Increase		

AVP, arginine vasopressin; CSF, cerebrospinal fluid; hCG, human chorionic gonadotropin; PST, pituitary stalk thickening

Di Iorgi N, et al. Best Pract Res Clin Endocrinol Metab. 2015;29:415-36.

CONCLUSIONS 1/2

- **Early aetiological diagnosis** of conditions presenting with polyuria and polydipsia is possible in the great majority of patients with CDI within the first 2 years
- **Tumour-associated pituitary stalk thickness** is not common in children younger than 5 years
- **MRI examination** every 6 months for 2 years is essential
  - Don’t miss at least MRI after 6 months!
- The identification of thick pituitary stalk (entire, proximal or distal) represents an **aspecific marker** of local lesion with an unpredictable evolution that needs a close, careful and long-term follow up
  - Pay attention to Anterior Pituitary size!!

CDI, central diabetes insipidus; MRI, magnetic resonance imaging

CONCLUSIONS 2/2

- **MRI STIR** technology is promising for the early identification of LCH-dependent CDI and **T2 Drive** may be helpful in the early diagnosis of germinoma
- **Surgical biopsy** must be reserved for selected cases
  - The recognition of “self-limited” or evolutive diseases is very important in terms of management and prognosis
- The number of anterior pituitary defects is associated with the severity of **PS involvement**
- **Long-term clinical and endocrine follow up** are needed and partial rescue of anterior function is possible
- Careful monitoring of signs or symptoms of **organ involvement by LCH** is recommended after the diagnosis of long-lasting idiopathic central diabetes insipidus

CDI, central diabetes insipidus; LCH, langerhans cell histiocytosis; MRI, magnetic resonance imaging; PS, pituitary stalk; STIR, short tau inversion recovery