Contrasting central diabetes insipidus due to preproAVP mutations : earlier onset of symptoms in recessive than in dominant forms

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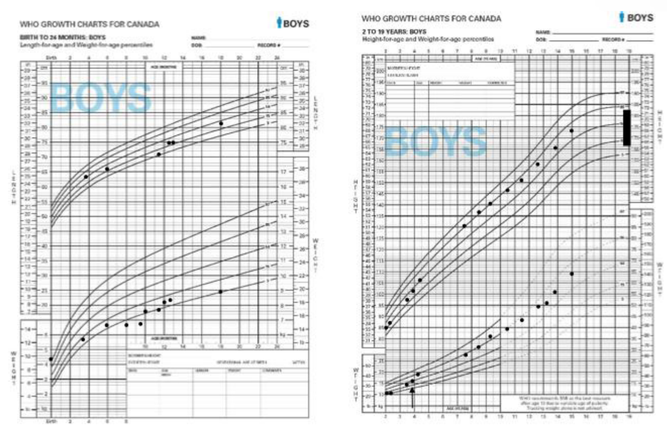
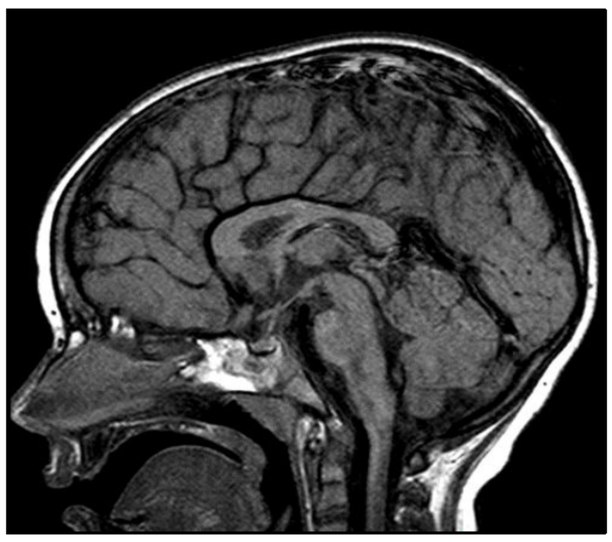
BACKGROUND

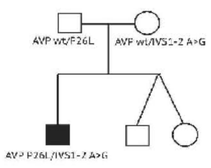
- Familial Central Diabetes Insipiduis : 0-7.5% of pediatric CDI.
- Genetic isolated CDI due to mutations in the AVP gene, mostly heterozygous and de novo or inherited in an autosomal dominant mode, onset of symptoms delayed until the third decade of life and the posterior pituitary hypertintense signal no longer visible on MRI.
- Only three pedigrees published with autosomal recessive inheritance and homozygous AVP mutations

CASE REPORT

- A four-year-old boy referred for longstanding polyuria and polydipsia.The mother is French-Canadian and the father Lebanese, no familial history of CDI.
- At 7 months, failure to thrive. Serum sodium = 145 mmol/L, urine specific gravity < 1005.
- At 4 years, after 4h of water deprivation, serum sodium 144 mmol/L, serum osmolality 314 mmol/kg and urinary osmolality 111 mmol/kg. Two hours after 2.5 mcg of DDAVP intranasally, urinary osmolarity 442 mOsm/kg.
- Chronic treatment with DDAVP resulted in the disappearance of polyuria/polydipsia and in catch-up growth to target.
- MRI : normal posterior pituitary hyperintense signal.
- ;*preproAVP* sequenced in the proband and in his asymptomatic parents : compound heterozygote, having inherited a novel A to G transition in the splice acceptor site of intron 1 (IVS1-2A>G) from his mother and the known P26L mutation from his father; the latter has been reported in the homozygous state in two inbred Middle-Eastern pedigrees.







DISCUSSION

- Recessive CI very rare with 3 papers describing consanguineous pedigrees
- Fist case published with two different mutations : the P26L mutation inherited from his Lebanese father and the ISV1-2A<G from his Fren Canadian mother
- Onset of symptoms early in life : consistent with bi-allelic inactivation of AVP, by contrast in dominant CDI age of onset older and more variable
- RMI : bright spot absent in dominant forms and sometimes present in recessive formsMaking a genetic diagnosis informs family counseling and eliminates the need for repeated MRI studies.

Ref.	Sex	Ethnicity	Age when symptoms 1st noticed	Posterior pituitary at MRI	Mutation
(5)	M	Palestinian	18 - 24 months	Absent	P26L/P26L
	M	Palestinian	24 months	Absent	P26L/P26L
	F	Palestinian	20 months	Present	P26L/P26L
(6)	F	Palestinian	6 weeks	Absent	P26L/P26L
	M	Palestinian	6 weeks	Absent	P26L/P26L
	M	Palestinian	6 weeks	Absent	P26L/P26L
(7)	M	Pakistani	N.R.	N.R.	del/del
	F	Pakistani	N.R.	N.R.	del/del
	F	Pakistani	N.R.	N.R.	del/del
	F	Pakistani	4 - 8 days	Absent	del/del
Present case	M	French Canadian /Lebanese	< 4 months	Present	IVS1-2A>G /P26L

Table. Clinical, radiological and molecular genetic characteristics of published patients with autosomal recessive central diabetes insipidus (N.R., not reported; del: deletion)

CONCLUSION

Autosomal recessive CDI : diagnosis to consider in an infant with a very early onset of symptoms and no brain malformation, even in the absence of consanguinity.

Aknowlegments

References
5. Willcutts MD et al, HumMolGenet. 1999
6. Abu Libdeh A et al, European journal of endocrinology 2010.
7. Christensen JH et al, Clinical genetics. 2013