

Cryptorchidism Is Commonly Observed in Allan Herndon Dudley Syndrome

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Background

- Allan-Herndon-Dudley syndrome (AHDS) is an X-linked mental retardation syndrome characterized by severe psychomotor retardation and pathognomonic thyroid parameters. Defects in monocarboxylate transporter 8 (MCT8), which facilitates thyroid hormone (TH) uptake and efflux across plasma membranes, have been linked to this disease.
- Schwartz et al. have reported the incidence of undescended testes as 8%.
 - Am J Hum Genet 77:41 (2005)

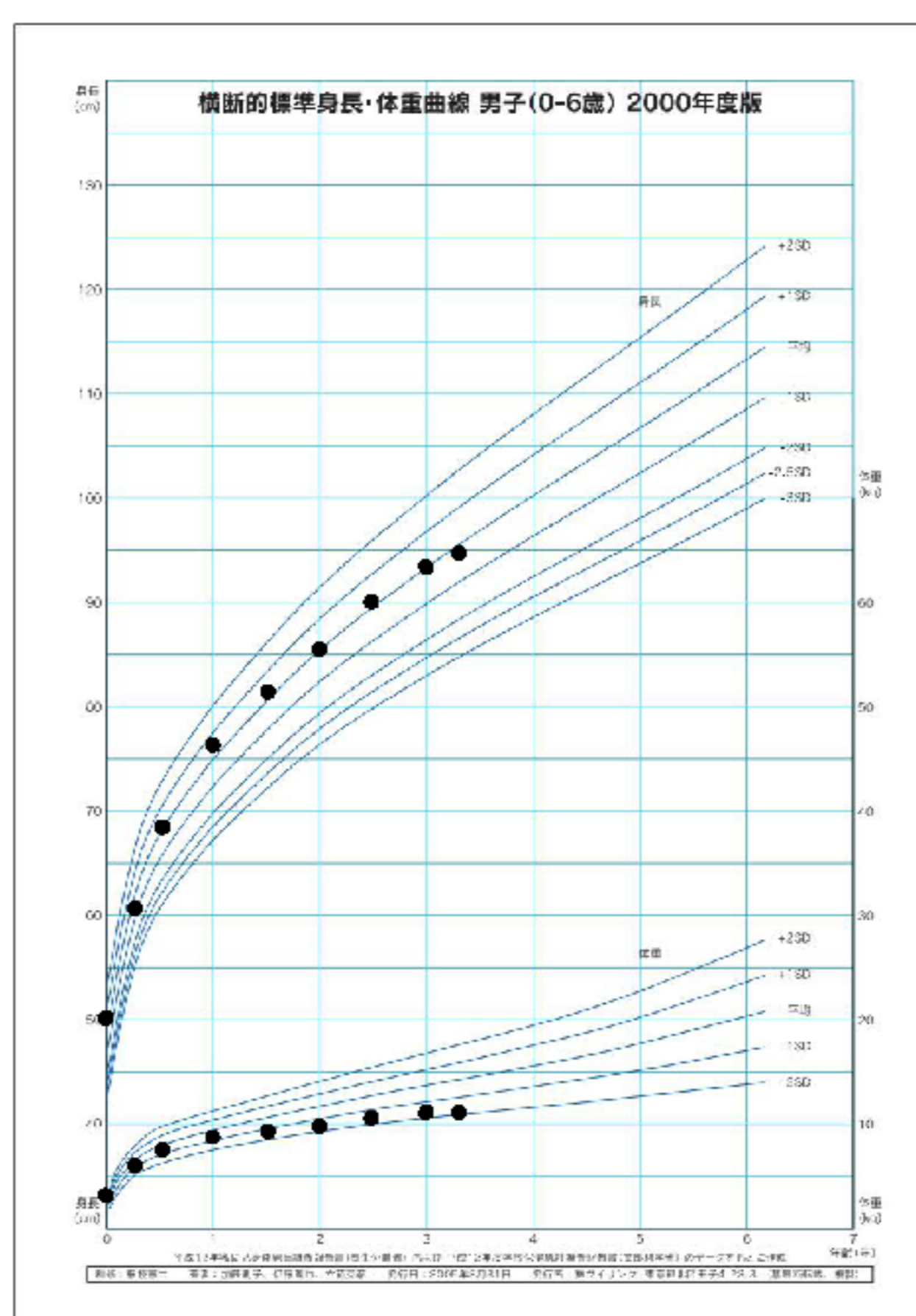
Case 4

- 3y3m old boy
- Birth history
 - The patient was born by normal spontaneous vaginal delivery after a 41w3d uncomplicated gestation. BW was 3254 g. There was no birth asphyxia and he received 48 h phototherapy for neonatal jaundice.
- Family history
 - No mental retardation or thyroid disorders
- Present history
 - Persistent head lag at age 5m prompted the primary care physician to refer the patient to our hospital. Thyroid function tests were: TSH 6.51 μ U/ml, fT4 0.69 ng/ml, fT3 8.29 pg/ml. Head MRI demonstrated delayed myelination. A p.G276R mutation in the *SLC16A2* gene established the diagnosis of AHDS.
- Physical examination and clinical course (testes)
 - On the first visit at age 6m, bilateral testes were 1~2 ml and palpable in the scrotum. At age 10m, ascending testes was noticed. Conservative observation was continued since the testes could be easily guided into the scrotum.
 - The testes became retractile by age 1y2m. The volume decreased to 1 ml and he was admitted for further examination at age 1y7m. Physical examination demonstrated bilateral testes in the inguinal canal. The testes position was determined as high scrotal and observation was continued.

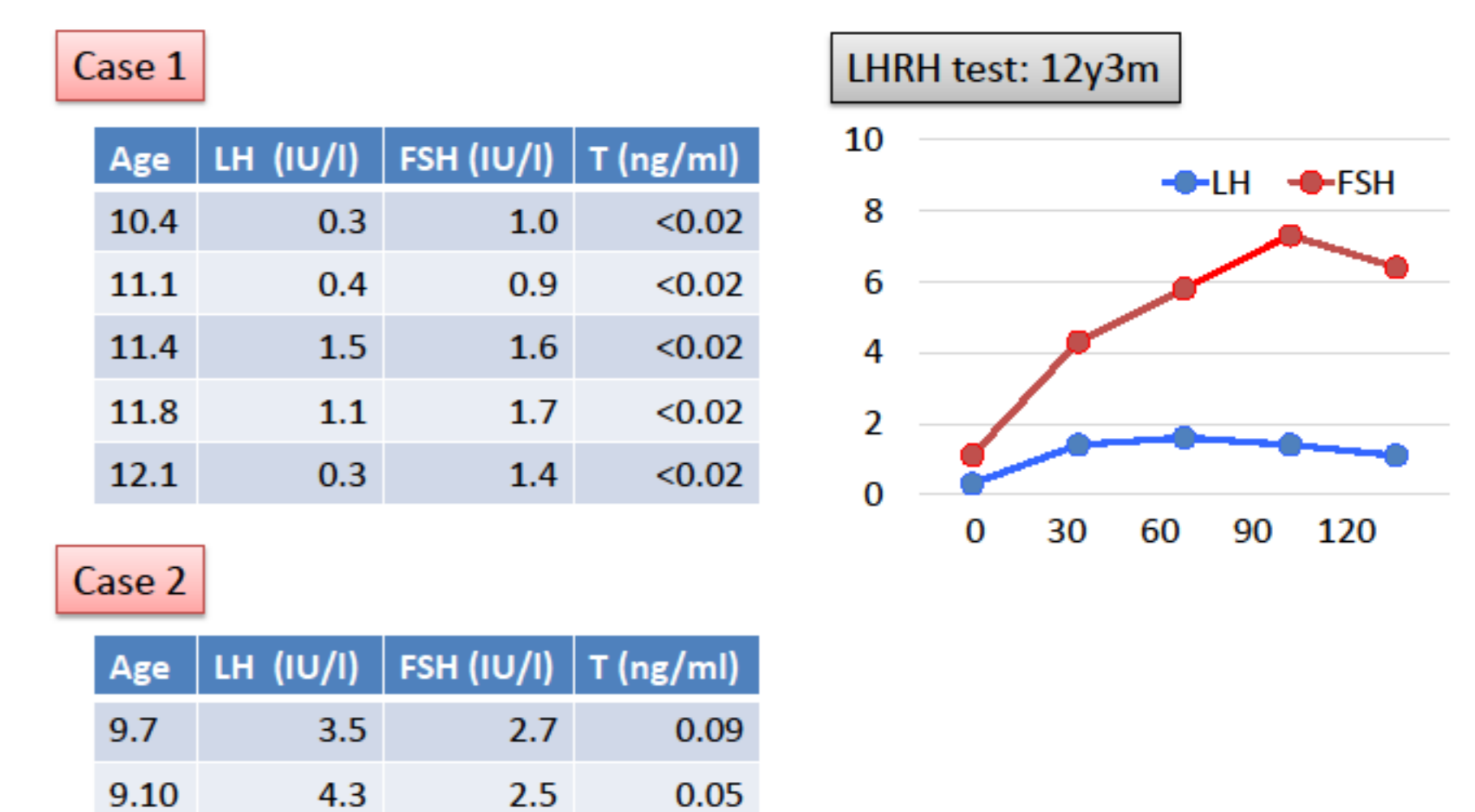
Endocrinological Data

Age	TSH	fT ₃	fT ₄	LH	FSH	T	IGF-1
	μ U/ml	pg/ml	ng/ml	IU/l	IU/l	ng/ml	ng/ml
0y5m	6.51	8.29	0.69				
0y6m	4.09	7.5	0.7	5.5	3.2	<0.05	78.3
1y0m	4.92	8.1	0.6				
1y5m	8.45	7.4	0.5				
1y7m	11.1	8	0.7	7.3	1.4	<0.05	59
2y7m	9.81	5.6	0.5	1.7	0.7		68
3y3m	6.57	6.4	0.7	0.6	0.8	<0.05	40

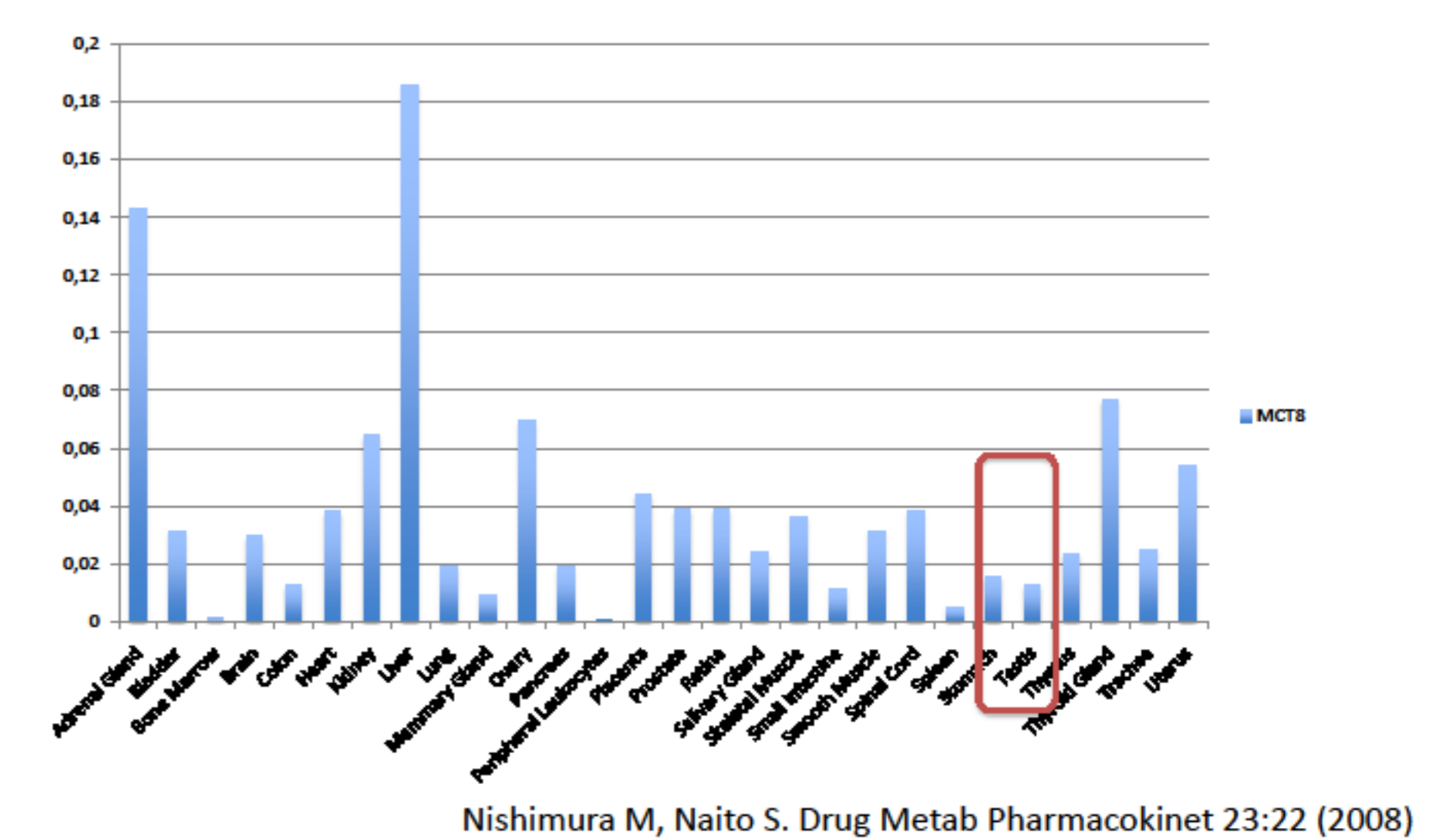
Growth Chart



HPG axis in Cases 1 & 2



MCT8 mRNA Expression in Humans



Effect of T₃ on the Testes

- | | |
|--|---|
| Sertoli cell <ul style="list-style-type: none"> Proliferation (-) Differentiation (+) ABP production (-) AR (+) Aromatase (-) Connexin 43 (+) ER (-) GLUT1 (+) IGF-1 (+) Inhibin (+) Lactate (+) NCAM (-) Nidogen (+) p21Cip1 (+) p27Kip1 (+) Testosterone metabolism aromatization (-) Type IV collagen (-) Vimentin phosphorylation (+) | Leydig cell <ul style="list-style-type: none"> Differentiation (+) Steroidogenesis (+) StAR protein (+) |
|--|---|
- ABP, androgen binding protein; AR, androgen receptor; ER, estrogen receptor; GLUT1, glucose transporter-1; IGF-1, insulin-like growth factor-1; NCAM, neural cell adhesion molecule.
- Gao Y et al. Front Endocrinol (Lausanne) 5:188 (2014)

Objective

- To determine whether the prevalence of cryptorchidism is higher in severely affected AHDS patients than previously reported.

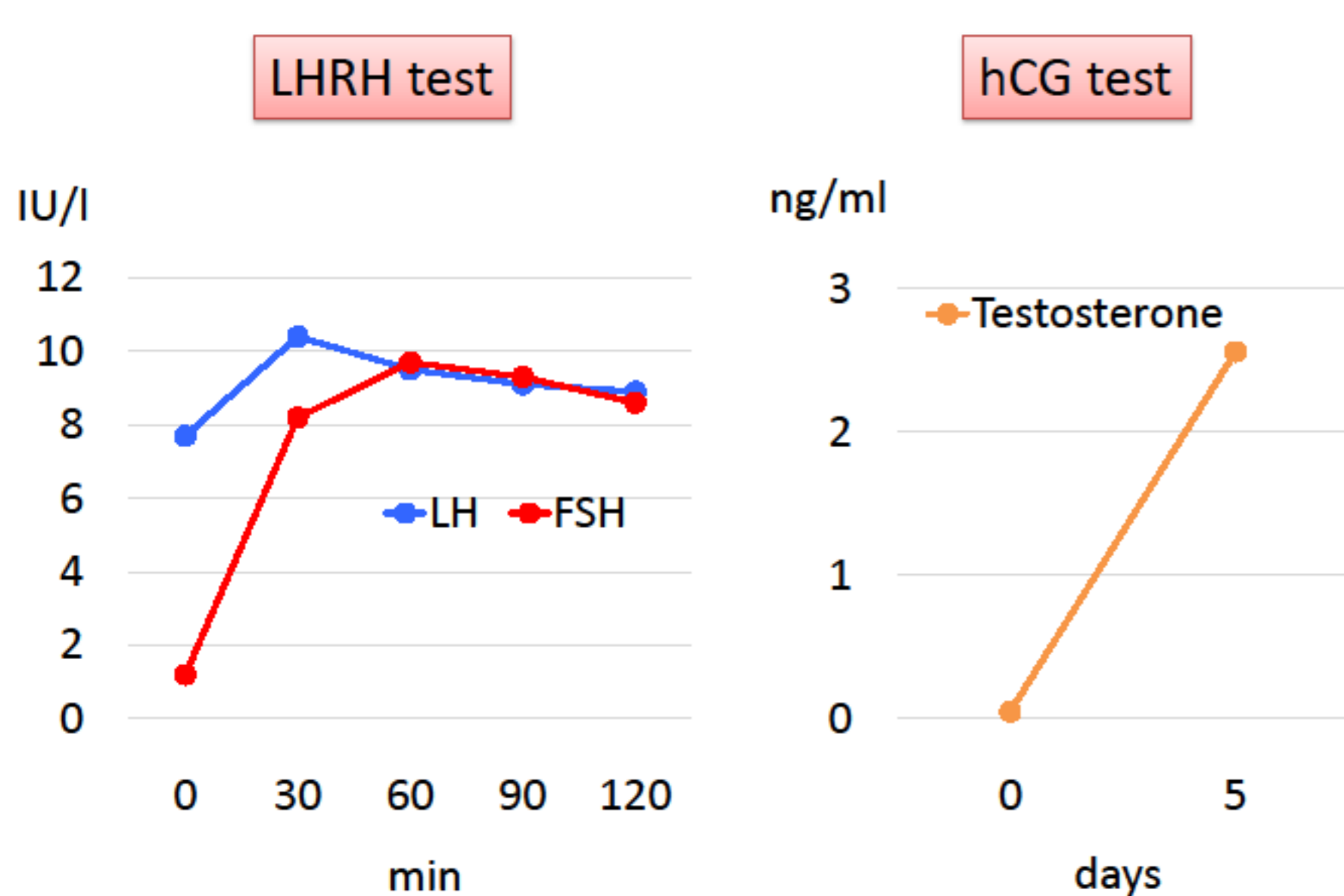
Patients and Methods

- A retrospective chart review of seven AHDS patients followed at our hospital was conducted.

Results

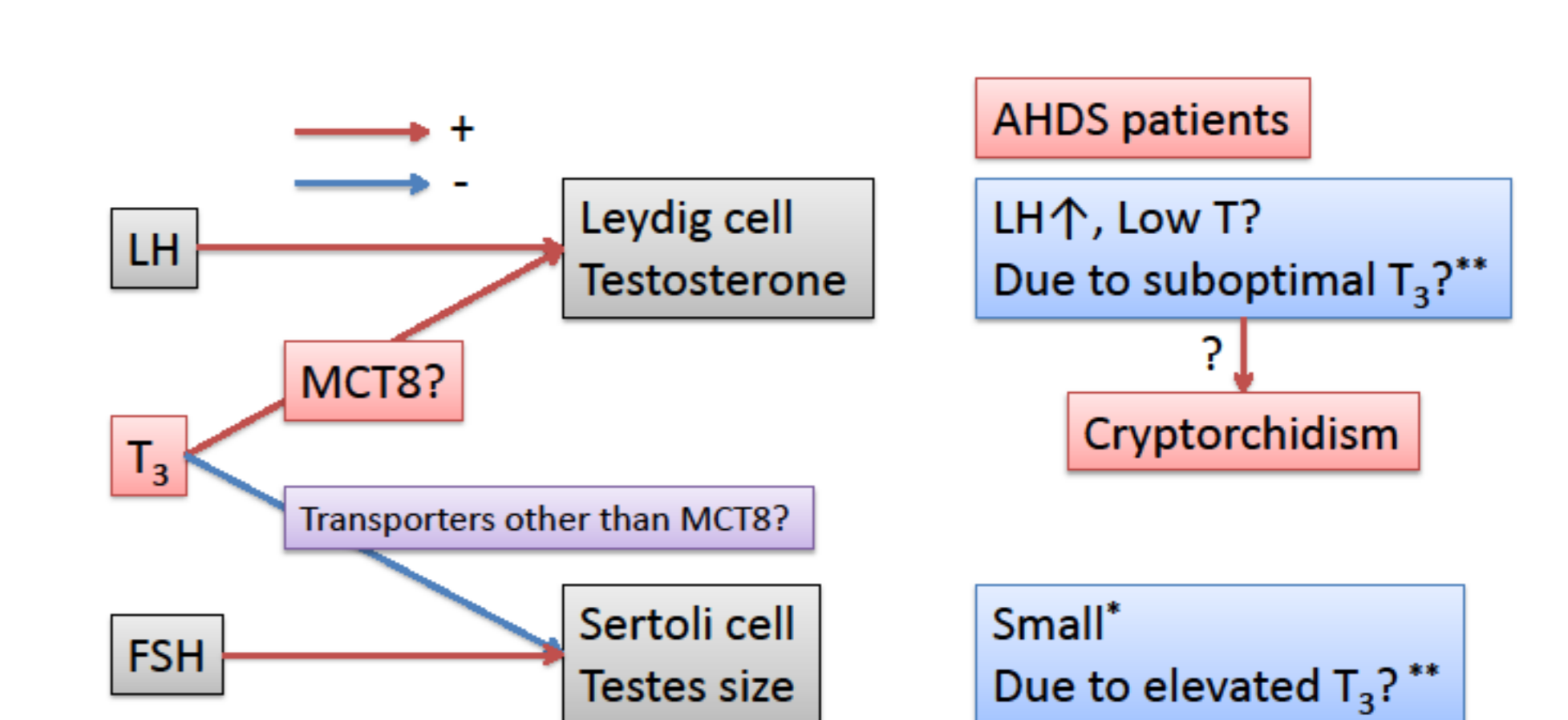
- Four out of seven AHDS patients had cryptorchidism. Another patient had severe retractile testes.

Case	Age (y)	Testes State	Orchidopexy	Size (ml)	Puberty
1	12	R: cryptorchidism L: retractile, inguinal	R: + L: -	2 (12y)	Tanner 1-2
2	10	R: cryptorchidism L: cryptorchidism	+	1-2 (5y)	Tanner 2?
3	4	R: cryptorchidism L: cryptorchidism	+	1-2 (2y)	Tanner 1
4	3	R: cryptorchidism L: cryptorchidism	+	1-2 (3y)	Tanner 1
5	7	R: retractile, inguinal L: retractile, inguinal	scheduled	1 (6y)	Tanner 1
6	8	R: retractile L: retractile, inguinal	-	1-2 (7y)	Tanner 1
7	4	R: retractile, inguinal L: retractile	-	1-2 (2y)	Tanner 1



- However, since they became inguinal, orchidopexy was performed at age 2y9m. The testes volume reverted to 1-2 ml by age 3y3m.

Postulated Mechanism



*Schwartz CE et al. Am J Hum Genet 77:41 (2005)
**Gao Y et al. Front Endocrinol 5:188 (2014)

- Elevated basal LH during mini-puberty/early puberty suggests suboptimal testosterone production and inability to sustain testicular descent in AHDS patients.
- This maybe due to insufficient T₃ action in Leydig cells as a result of MCT8 deficiency.
- Spasticity of the cremaster muscle may also play a part in testicular ascension.
 - Smith JA et al. J Pediatr Surg 24:1303 (1989)

Conclusions

- 5/7 of the patients with severe AHDS presented cryptorchidism or retractile testes requiring orchidopexy.
- Sufficient TH transport may be necessary to sustain testicular descent.
- Early detection is needed to avoid the complications of cryptorchidism.