Long-Term Outcome In Leydig Cell Hypoplasia

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Background

Leydig Cell Hypoplasia (LCH) is a very rare form of a Disorder of Sex Development (DSD).

This condition is caused by homozygous inactivating variants in the LHCGR gene with a wide spectrum of phenotypes, ranging from completely female external genitalia to male genitalia.

Given the rarity of this condition, long-term outcome in these patients is unclear.

Objectives

To assess sex assignment, clinical characteristics and long-term outcome of 46,XY LCH cases.

Methods

Through the international DSD (I-DSD) Registry and its users, clinical information on first and last presentation was gathered on 46,XY LCH cases born before 2004.

A questionnaire was sent to each clinician at these centres to collect information on long-term health.

Data collection was focused on:

- **Clinical features at first and last assessment (i.e. pubertal status)**
- **Laboratory and genetic findings**
- **Psychological support**
- **Long-term documented outcomes**

The external masculinisation score (EMS) was used as a composite score to describe the external genitalia.

Results

Only 17 cases out of 3.803 records in the I-DSD Registry had a confirmed diagnosis of 46,XY LCH and were about or over 14 years.

Frist assessment:

- **Median age was 17 years (range 8 days, 45 years).**
- **Median EMS, out of 12, in those raised as males and females was 5 (range 5, 6) and 2 (range 1, 5), respectively (p=0.023).**
- **The diagnosis was reached through clinical biochemistry in all, and confirmed by genetics in 13 cases.**

Cases raised as boys were likely to experience more surgery and median age at last repair of hypospadias was 5.8 years (2, 8.4).

Median age at bilateral gonadectomy in those raised as girls was 17.9 years (2.2, 46).

At last assessment:

- **Undermasculinisation was observed in all males with median EMS of 9.**
- **Weight SDS and BMI were significantly higher in female cases (p-value 0.009 and 0.024, respectively), although median BMI was within the normal range.**
- **Using the current gender assigned, height was >2SD in 3 female cases (not using the growth chart according to karyotype).**
- **Of the 17 cases, DXA was performed in 8 (47%) and 7/8 (88%) exhibited osteopenia/osteoporosis.**

Psychological support was provided in 16/17 (94%).

- **2/17 (12%) cases were reported to have undergone gender reassignment: one from female to male at 5.3 years, and the other from male to female at 17 years.**

Results

Table 1. Clinical features and long-term outcomes of 46,XY LCH cases

MOST RECENT ASSESSMENT				LONG-TERM HEALTH		
Gender	Age (years)	EMS	Tanner Stage	HRT	Surgery (n)	Outcomes
M	18,9	6	3	No	H Repair (2)	Micropenis, H
M	7,7*	9	1	No	H Repair (1)	Micropenis
M	18,3	9	4	No	H Repair (4)	Micropenis, Azoospermia, Osteoporosis
M	13.5**	9	2	No	H Repair (2)	Micropenis
F	16.1*	0	1	No	Gonadectomy	-
F	13,8	0	2	Oestrogens	Gonadectomy	Osteopenia
F	28	0	5	No	Gonadectomy	MetS, Obesity, Osteopenia
F	19,9	0	1	Oestrogens	Gonadectomy, waiting for vaginoplasty	-
F	25.8	0	5	Oestrogens	Gonadectomy	Hair loss and mood swings
F	59	0	5	Oestrogens	Gonadectomy	MetS, Obesity, Osteoporosis
F	62	0	5	Oestrogens	Gonadectomy	Osteoporosis
F	19.7	0	4	Oestrogens	Gonadectomy	-
F	47	0	5	Oestrogens	Gonadectomy	Osteopenia
F	14	0	4	Oestrogens	Gonadectomy	-
F	62**	0	4	Oestrogens	Gonadectomy	Hypothyroidism, Obesity
F	51	0	5	Oestrogens	Gonadectomy	Osteopenia, Type 2 Diabetes
F	41	0	4	Oestrogens	Gonadectomy	Asthma

F: Female; H:Hypospadias; HRT: hormonal replacement therapy;
M: Male; MetS: Metabolic Syndrome
** Lost at follow-up* *** Cases reassigned*

Discussion

- **With the advent of the I-DSD Registry and its related network a study of the long-term outcomes of rare conditions such as LCH has now become feasible.**
- **Children with LCH can present with a variable level of undermasculinisation and are more likely to be raised as females but gender reassignment may be necessary in some cases.**
- **Bone health, obesity and metabolic disorders are not uncommon issues among LCH cases.**

Conclusion

Irrespective of sex assignment, young adults with LCH may continue to exhibit hypogonadism and associated co-morbidities.

A standardized approach for management and monitoring of clinical outcomes is required.