Long-term clinical course in three patients with MAMLD1 mutations

Yasuko Fujisawa1), Maki Fukami2), Tomonobu Hasegawa3), Ayumi Uematsu4), Koji Muroya5) and Tsutomu Ogata1)

1) Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan
2) Department of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo 157-8582, Japan
3) Department of Pediatrics, Keio University School of Medicine, Tokyo 160-8582, Japan
4) Department of Endocrinology and Metabolism Unit, Shizuoka Children’s Hospital, Shizuoka 420-8660, Japan
5) Department of Endocrinology and Metabolism, Kanagawa Children’s Medical Center, Yokohama 232-8555, Japan

Abstract. Although MAMLD1 on chromosome Xq28 is known as a causative gene for 46,XY disorders of sex development, clinical information is virtually limited in patients of infancy to early childhood. Here, we report long-term genital and hormonal findings in three previously described Japanese patients with MAMLD1 mutations, i.e., patients 1 and 2 with p.E197X and patient 3 with p.R726X. As previously reported, patients 1–3 exhibited penoscrotal hypospadias with chordee, microphallus, bifid/hypoplastic scrotum, and/or bilateral cryptorchidism/retractile testes, in the presence of sufficiently high serum basal or hCG-stimulated testosterone values in the mini-pubertal period to early childhood. Subsequently, patient 1 had low serum hCG-stimulated testosterone value (126 ng/dL) at 13 11/12 years of age, and manifested microphallus (4.5 cm), relatively small testes (left 8 mL and right 10 mL), Tanner stage 3 genitalia and pubic hair development at 18 3/12 years of age. Similarly, patients 2 and 3 showed mild hypergonadotropic hypogonadism at 7 0/12 and 9 9/12 years of age, respectively, with serum GnRH-stimulated LH values of 5.5 and 7.2 mIU/mL and FSH values of 10.3 and 19.8 mIU/mL and hCG-stimulated testosterone values of 70 and 80 ng/dL, respectively. Testis ultrasound studies delineated microlithiasis in patients 1 and 3. These results imply for the first time deterioration of testicular function with age in patients with pathologic MAMLD1 mutations.

Keywords: MAMLD1, 46,XY DSD, Clinical course, Testicular function, Deterioration
mutations were assessed as amorphic mutations.

Genital findings in early infancy of patients 1–3, and endocrine findings up to 2 5/12 years in patient 1 and 2 and 6 3/12 years of age in patient 3, have been described previously [1]. In brief, patients 1–3 exhibited penoscrotal hypospadias with chordee, microphallus, and bifid scrotum, and patients 1 and 3 also had bilateral cryptorchidism and retractile testes, respectively. Thus, they received urethroplasty and/or orchiopexy. Basal and/or GnRH- or hCG-stimulated LH, FSH, T, and dihydrotestosterone values were apparently normal. In particular, hCG-stimulated serum T was 250 ng/dL in patient 1 at 2 6/12 years of age (normal range [NR] > 200 ng/dL) [10], and basal T was 260 ng/dL in patient 2 at one month of age (NR, 59 – 408 ng/dL) [11] and 270 ng/dL in patient 3 at three months of age (NR, 3 – 349 ng/dL) [11].

However, patients 1–3 manifested primary hypogonadism in later ages (Table 1). Patient 1 exhibited incomplete secondary sexual development with microphallus and relatively small testes in the pubertal period. Patients 2 and 3, though they were still in their prepubertal period, showed borderline to definite microphallus. The GnRH-stimulated LH and/or FSH values were mildly elevated in patients 2 and 3, and the hCG-stimulated T values were obviously low in patients 1–3. Furthermore, testis ultrasound studies delineated microlithiasis in patients 1 and 3, but not in patient 2 (Fig. 1).

Table 1 Genital and endocrine findings in three male patients with MAMLD1 nonsense mutations

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<tr>
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<tr>
<td><strong>&lt;Genital findings&gt;</strong></td>
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<td></td>
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<tr>
<td>Age at exam. (y:m)</td>
<td>13:11</td>
<td>7:00</td>
<td>6:03</td>
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<tr>
<td>Tanner stage</td>
<td>Genitalia 1, Pubic hair 1</td>
<td>Genitalia 1, Pubic hair 1</td>
<td>Genitalia 1, Pubic hair 1</td>
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<tr>
<td>Penile length (cm)</td>
<td>Not examined</td>
<td>3.5 (3.4 – 5.8)</td>
<td>3.2 (3.4 – 5.7)</td>
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<tr>
<td>Testis size (mL)</td>
<td>3 (bilateral) (8 – 20)</td>
<td>2 (bilateral) (1 – 2)</td>
<td>1.5 (bilateral) (1 – 2)</td>
</tr>
<tr>
<td><strong>&lt;Serum hormone values&gt;</strong></td>
<td></td>
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<tr>
<td>Age at exam. (y:m)</td>
<td>13:11</td>
<td>7:00</td>
<td>9:09</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>Not examined</td>
<td>0.2 (0.2 – 1.9) → 5.5 (1.1 – 6.0) a</td>
<td>0.5 (0.2 – 1.9) → 7.2 (1.1 – 6.0) a</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>Not examined</td>
<td>1.3 (&lt;0.3 – 2.4) → 10.3 (1.9 – 7.6) a</td>
<td>5.0 (&lt;0.3 – 2.4) → 19.8 (1.9 – 7.6) a</td>
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<td>T (ng/dL)</td>
<td>12 (10 – 96) → 126 (&gt; 200) b</td>
<td>12 (3 – 13) → 70 (&gt; 200) b</td>
<td>28 (3 – 13) → 80 (&gt; 200) b</td>
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a Basal and peak values during a GnRH test (100 µg/m² [max. 100 µg] bolus i.v.; blood sampling at 0, 30, 60, 90, and 120 min). b Basal and stimulated values in an hCG test (3,000 IU/m²/dose [max. 5,000 IU] i.m. for three consecutive days; blood sampling on days 1 and 4). The values in parentheses represent the age-matched normal range [10–13].
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Development and weak Mamld1 expression in postnatal testes [1]; (ii) significantly reduced expression levels of Leydig cell-specific, but not Sertoli-cell specific, genes in the late fetal life of Mamld1 knockout mice [8]; (iii) compromised T production (~50%) by Mamld1 knockdown [9]; and (iv) positive human MAMLD1 expression in fetal and adult testes [2].

These findings would postulate several possibilities. First, MAMLD1 deficiency may compromise fetal Leydig cell function around the critical period for sex development, leading to 46,XY DSD with hypospadias because of reduced but not abolished T production, as has been proposed previously [1]. In this regard, recent mouse studies have indicated that prenatal T biosynthesis requires both fetal Leydig cells that produce ∆4-androstenedione and Sertoli cells that express Hsd17b3 for the conversion of ∆4-androstenedione into T [20], although such Sertoli cell-specific HSD17B3 expression has not been demonstrated in human fetuses. Thus, in contrast to Mamld1 knockout mice [8], if Sertoli cell function is also compromised in affected patients, this would also contribute to defective T production during fetal life of affected patients. Second, long-term MAMLD1 deficiency may gradually affect adult Leydig cell function, resulting in compromised T production with age. This notion

Discussion

This study showed for the first time deterioration of testicular function with age in patients with pathologic MAMLD1 mutations. Indeed, small testes during the pubertal period in patient 1 would imply spermatogenic impairment [14], and poor T responses to hCG stimulation and/or mild hypergonadotropinism in patients 1–3 would argue for adult Leydig cell dysfunction [14, 15]. In addition, testicular microlithiatis in patients 1 and 3 may also imply the presence of non-specific testicular dysfunction, because it is often found in subjects with testicular tumors and spermatogenic failure as well as in patients with hypogonadism-associated disorders such as Down syndrome and Klinefelter syndrome [16–19]. Thus, the present data, in conjunction with the previous findings [1], suggest that MAMLD1 deficiency causes 46,XY DSD during the fetal life and, while it permits apparently normal T production in infancy to early childhood, results in deterioration of testicular function with compromised T production from mid-childhood.

Several findings are worth pointing out with respect to the biological function of MAMLD1/Mamld1. They include: (i) clear mouse Mamld1 expression in Sertoli and Leydig cells during the critical period for fetal sex development and weak Mamld1 expression in postnatal testes [1]; (ii) significantly reduced expression levels of Leydig cell-specific, but not Sertoli-cell specific, genes in the late fetal life of Mamld1 knockout mice [8]; (iii) compromised T production (~50%) by Mamld1 knockdown [9]; and (iv) positive human MAMLD1 expression in fetal and adult testes [2].

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Fig. 1 Testis ultrasound images, showing microlithiasis in patients 1 and 3, but not in patient 2.
assumes that MAMLD1 plays a critical role in the functional maintenance rather than the development of adult Leydig cells [15], and would explain why T production can be preserved in the mini-pubertal period and in the early childhood. Spermatogenesis requires sufficient T production and normal Sertoli cell function [14]. If Sertoli cell function is also compromised with age in patients with MAMLD1 mutations, this factor, together with reduced T production, would contribute to defective spermatogenesis.

Two points should be made with regard to the present study. First, the apparently normal T values in infancy to early childhood (< 3 years of age) may not necessarily argue against the presence of hypogonadism. Indeed, there are no objective clinical indicators for hypogonadism in such a period, and serum T values may overlap between control boys and patients with incomplete/mild testicular dysfunction. In support of this notion, apparently normal serum T values in infancy to early childhood and declined serum T values in later ages have occasionally been reported in patients with incomplete/mild hypogonadism-associated disorders such as Prader-Willi syndrome, Down syndrome, and Klinefelter syndrome [21–23]. Second, while Maml1 knockout male mice have been produced [8], they would not serve as good models to examine the age-dependent deterioration of testicular function. Although Maml1 knockout male mice have reduced expression levels of Leydig cell-specific genes in the late fetal life, they have morphologically normal internal and external genitalia in the late fetal life, normal intra-testicular T values in the late fetal life and at 8 weeks of age, and normal reproductive capacity in adulthood [8 and our unpublished data]. Thus, further longitudinal clinical studies are required to determine whether the testicular function deteriorates with age in patients with MAMLD1 mutations.

Despite such caveats, the present study provides useful information for the testicular function in MAMLD1 mutation positive patients. Although the number of patients observed for a long time is quite limited, this study suggests age-dependent deterioration of testicular function in patients with MAMLD1 mutations.

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References

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