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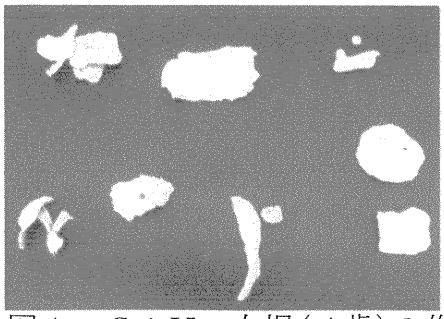
図１～５



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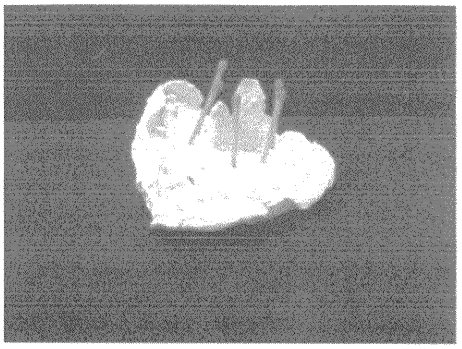

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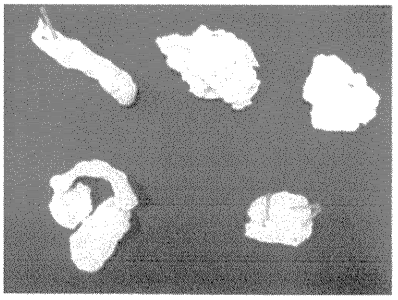

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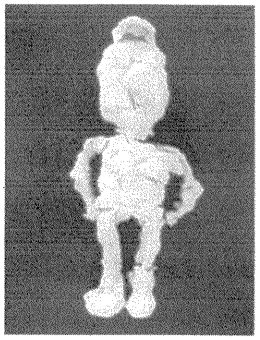

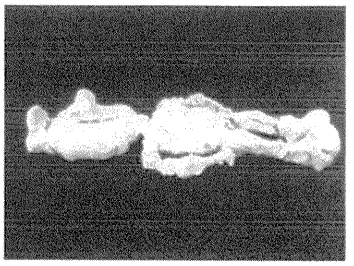

図４　ＰＯＲ欠損症，女児（７歳）の作品（左：上から撮影，右：横から撮影）

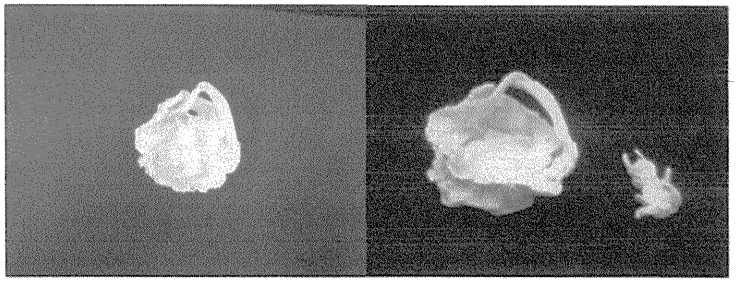

図５　卵精巣性ＤＳＤ，女児（６歳）の作品

Case Report

Effect of Excess Estrogen on Breast and External Genitalia Development in Growth Hormone Deficiency

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ABSTRACT

Background: The progress of sexual maturation and development in cases with growth hormone (GH) and insulin-like growth factor-I (IGF-I) deficiency is not well documented in females.

Case: We observed breast and genitalia development in a 2-year-old girl with GH deficiency following neonatal asphyxia; this girl later developed central precocious puberty. Markedly pigmented stimulated areolas and nipples without an apparent breast mound, and non-enlarged labia minora in the external genitalia were observed as features of sexual maturation in the patient. The hormonal condition was characterized by increased circulating estradiol levels and extremely low IGF-I levels.

Summary and Conclusion: This case indicates that IGF-I is necessary for exerting the full effect of estrogen on the development of breasts and maturation of external genitalia.

Key Words: Estrogen excess, Growth hormone deficiency, IGF-I deficiency, Breast development, Female genitalia development

Introduction

The progress of sexual maturation and development in cases with growth hormone (GH) and insulin-like growth factor-I (IGF-I) deficiency is better documented in males than females. It has been demonstrated that congenital GH deficiency is associated with the development of a micropenis, which shows that GH has an intrauterine effect on genital development.[1] Observations in female patients with Laron syndrome, which is a unique human condition with genetically determined GH insensitivity and subsequent IGF-I deficiency, have revealed delay of both sexual development and maturation, but patients eventually attain full development.[2] However, to our knowledge, there have been no studies of cases with a similar hormonal status produced by acquired causes.

Case

The patient was a girl aged 1 year and 6 months who had neurologic consequences of developmental disability following perinatal asphyxia and who developed bilateral darkened areola. She was born at 37 weeks of gestational age with a birth weight of 2700 g and severe asphyxia. Magnetic resonance imaging (MRI) revealed marked cerebral atrophy, but the pituitary gland and stalk were visible in mid-sagittal T1-weighted MRI.

Darkened areola appeared, but with no apparent breast mounds. Laboratory tests showed a circulating estradiol (E2) level of 88 pg/mL (normal prepubertal level < 10 pg/mL), luteinizing hormone (LH) 1.75 mIU/mL (normal prepubertal level < 0.18 mIU/mL), and follicle-stimulating hormone (FSH) 7.12 mIU/mL (normal prepubertal level < 4.2 mIU/mL), indicating an enhanced hypothalamic-pituitary-gonadal axis. Plasma total protein and IGF-I concentrations were 6.0 g/dL (normal 5.0-6.8 g/dL) and 9 ng/mL (normal for age 35-88 ng/mL), respectively. The IGF-I level was considered to be markedly depressed, since increased E2 enhances the GH-IGF-I axis. A diagnosis of central precocious puberty as a consequence of hypoxic brain encephalopathy was made, but gonadal suppression therapy was not commenced.

At 2 years and 2 months old, her height was 75 cm and weight 11 kg. Images of breasts and genitalia are shown in Figures 1 and 2. The breasts showed markedly enlarged areola and nipples with prominent darkening, but without formation of a breast mound. Firm breast tissue was palpable under the areola. In the external genitalia, the labia minora was 8 mm long (the 50th percentile size at this age is 9 mm),[3] showing no apparent enlargement. The hymen appeared to be thickened. There was no vaginal discharge or bleeding. Breast ultrasonography revealed glandular buds (right side 9 × 17 mm, left 9 × 13 mm) associated with poorly developed fatty stromal tissue. A pelvic ultrasound examination visualized both ovaries with small multicystic characteristics and a uterus with tubular formation.

The circulating estradiol level was 66 pg/mL, and IGF-I was 18 ng/mL. The LH and FSH responses to stimulation with gonadotropin-releasing hormone showed a pubertal pattern: LH from a basal level of 2.94 mIU/mL to a peak level of 30.3 mIU/mL, and FSH from a basal level of 6.5 mIU/mL to 11.7 mIU/mL. Growth hormone responded poorly to glucagon stimulation, with a change from 0.3 to 0.8 ng/mL. Other pituitary hormones including prolactin, thyroid-stimulating hormone, and adrenocorticotropic hormone

The authors indicate no conflicts of interest.

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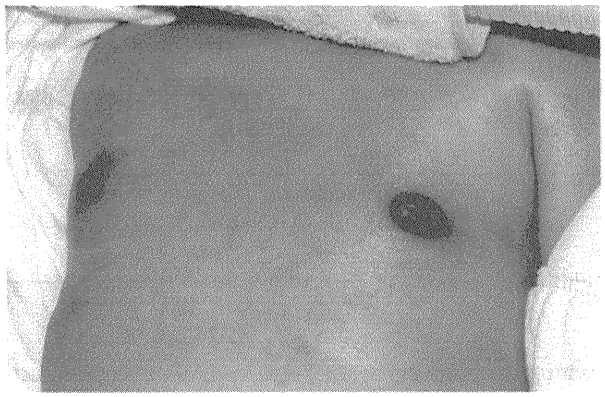

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Figure 1. Breast development at 2 years and 2 months showing clearly enlarged areola and nipples with prominent darkening, but no apparent breast mounds.

were normal. Bone age was 2 years of age using the Greulich- Pyle method, almost the same as the chronological age.

Summary and Conclusion

An increased incidence of GH deficiency resulting from neonatal asphyxia is well established, and neonatal encephalopathy has occasionally been found to lead to development of central precocious puberty.[4] Our patient had GH deficiency as a result of neonatal asphyxia and later developed central precocious puberty, with hormonal conditions of increased circulating levels of E2 and decreased levels of IGF-I. The ultrasonographic appearance of the ovaries indicated that IGF-I may not be essential for gonadotropin secretion and subsequent follicular development in the ovary, although GH replacement therapy may ameliorate fertility in some cases of GH deficiency.[5]

There is considerable evidence that GH and systemic and locally produced IGF-I exert stimulatory synergistic or permissive effects at each level of the hypothalamic-pituitary-gonadal axis in the reproductive tract, external genitalia, and mammary gland. Maturing at a normal age and reaching full reproductive potential requires the actions of GH and an adequate IGF-I level in the peripheral circulation, in addition to increased sex steroids during puberty.[6]

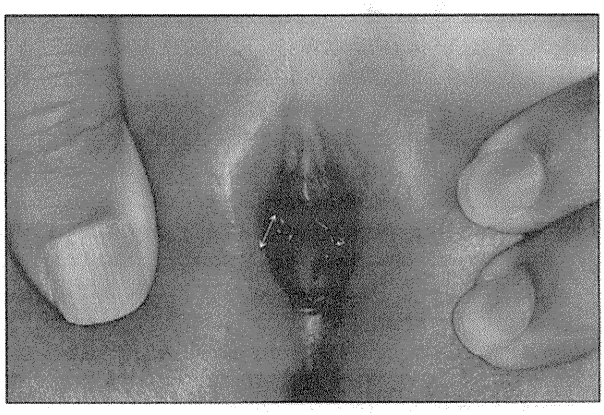

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Figure 2. External genitalia at 2 years and 2 months showing no apparent enlargement of the labia minora (the arrow indicates the length of the labia minora). An annular thickened hymen with notches is apparent.

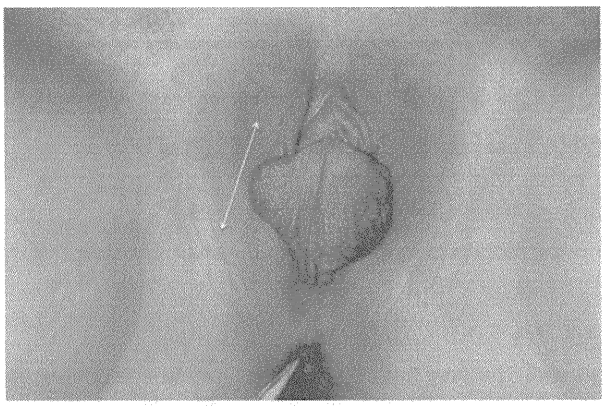

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Figure 3. External genitalia of a 5-year-old patient with ovarian granulosa cell tumor (we have previously described this case,[10] but the image was not presented in the article). A high circulating estradiol level enhanced growth of the labia minora (indicated by an arrow).

Laron syndrome, or primary GH insensitivity, is a useful model for studying the effects of congenital IGF-I deficiency. Female patients with Laron syndrome have small genitalia and delayed puberty, but they eventually reach full sexual development and normal reproductive ability, which implies that IGF-I in concert with sex hormones has a modulatory but not essential function on female sexual development and maturation.[2] Estrogen stimulates growth of the nipples, progression of mammary duct branching to the stage at which ductiles are formed, and fatty stromal growth until it constitutes about 85% of the mass of the breast. Growth hormone (via IGF-I) and glucocorticoids are thought to play permissive roles in these processes.[7] Pigmented stimulated areolae and nipples are hallmarks of estrogen excess.[8]

Estrogen receptor is also present in the labia minora,[9] but in the present case, the labia minora failed to grow despite exposure to excess estrogen. This finding indicates that IGF-I is essential for development of the labia minora, and it is of note that maturation of the labia minora is reported to be delayed in Laron syndrome.[2] To contrast our findings with the natural response of the labia minora to exposure to a high concentration of estrogen in a prepubertal girl with normal IGF-I, we show an image of a hugely enlarged labia minora of a different patient (Figure 3).[10] In the patient described in the current report, the thickened hymen was consistent with the elevated level of circulating estradiol. Hymenal morphology is dependent on estrogen status,[11] and thus it seems that GH deficiency has no influence on hymenal growth.

In conclusion, in the present case of a GH-deficient female infant with excess estrogen as a result of precocious puberty, it appears that IGF-I is necessary for exerting the full effect of estrogen on the development of breasts and maturation of external genitalia.

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REVIEW PAPER

Chromosome Analysis Using Spectral Karyotyping (SKY)

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Abstract Spectral karyotyping is a novel technique for chromosome analysis that has been developed based on the approach of the fluorescence in situ hybridization technique. Spectral karyotyping makes it feasible to diagnose a variety of diseases, because of its technology in painting each of the 24 human chromosomes with different colors. In recent years, it has become possible to adopt the usage of spectral karyotyping for research in general clinical practice, and its usability has attracted particular attention in the diagnosis of different diseases. In this review, we will explain the principle of the spectral karyotyping, as well as its specificity and limitation in detecting the genetic defects within clinical application by presenting two case reports.

Keywords Spectral karyotyping · Fluorescent in situ hybridization · Chromosome SKY · Multicolor FISH

Introduction

The first report of human chromosomes was made in 1882 by Flemming, in which 22–28 chromosomes in the dividing cells of the corneal epithelium were described [1]. Forty years later, Painter reported that the number of human chromosomes was 48 and that sex was determined according to the presence or absence of the Y chromosome [1]. It was not until the report of "$2n = 46$" was made in 1956 by Tjio and Levan that the nature of human chromosomes was further established [1]. Following this report, the relationships between various congenital disorders and chromosomal abnormalities have been revealed one after another. In 1959, Lejeune et al. [2] demonstrated that Down syndrome is caused by the presence of an extra chromosome 21, i.e., trisomy [3]. This finding of chromosome 21-trisomy was a turning point in the subsequent discovery of several other trisomy syndromes, including chromosomes 18 [4, 5], 13 [6], 8 [7], and 22 [8, 9]. Besides the chromosomal number aberrations, abnormalities associated with sex chromosomes, viz., Turner syndrome [10] and Klinefelter syndrome [11] and other chromosomes [5, 12] have been reported.

An increased understanding of malignant diseases in the 1960s and the advent of better cell culture methods including a method of culturing peripheral blood [13] led to the first discovery of chromosomal abnormalities in malignant tumors, the Ph^1 chromosome, which is specific to chronic myelogenous leukemia [14]. Genetic analysis studies, represented by the Human Genomic Project [15], led to the application of modern genetics tools in research in biological phenomena such as the development, evolution, and aging, as well as abnormal cellular differentiation including cancers.

Therefore, in the course of studying human chromosomes for more than a century, many new techniques have been developed for chromosome testing. In 1971, Caspersson, et al. [16] developed Q-staining using quinacrine mustard, a fluorescent dye that binds to DNA, which was instrumental in the discovery that chromosomes have banding patterns (stripes). Later, improved staining techniques, including R-, T-, C-, and G-staining, have appeared. The analysis of the band has further advanced and now it has been developed into high-resolution chromosome banding [17]. Furthermore, along with the development of the fluorescent in situ hybridization (FISH)

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technique [18], which involves the mapping of a chromosome using fluorescent labeled probe, it has become possible to identify chromosomal microdeletion and structural abnormalities such as the extra portion of a chromosome and a marker chromosome. FISH has also been used in diagnosing abnormalities, caused by chromosomal aneuploidy—which are difficult to detect via conventional test methods.

Comparative genomic hybridization (CGH) [19] and spectral karyotyping (SKY) [20], which are based on the FISH technique, are relatively recent and improved techniques of chromosomal analysis. SKY as described here refers to the multicolor-FISH technique, which makes it possible to identify 24 human chromosomes via single hybridization and then to stain them with different colors. In this article, the analysis of chromosomal abnormalities using the SKY technique and its limitation for detection will be discussed.

Principle of SKY

Two techniques are used as the basic principles of FISH: chromosome painting and multicolor fluorescence. The former is a technique of drawing an entire image of certain chromosome by using fluorescent signals. The latter is a technique of drawing images of several hybridization signals with different florescent dyes. Combining these two techniques, in 1996, the SKY technique was developed by Schrock et al. [20].

In SKY, the color emission of chromosomes is determined by the combination of painting probes and (fluorescent dyes). In this technique, new colors can be developed by extracting a pair of different fluorescent dyes from among the five types of fluorescent dyes, spectrum orange, Texas red, Cy5, spectrum green, Cy5.5, and mixing each pair together. Thus, it is theoretically possible to create 2^N-1 number of colors from N types of fluorescent dyes. Therefore, 31 types of colors can be created from five types of fluorescent dyes. In reality, however, because some fluorescence has a wavelength close to that within the infrared spectrum, a two-dimensional imaging spectroscopy system (e.g., the Spectral Bio-Imaging System SD-200, Applied Spectral Imaging Ltd. Israel) needs to be used to process spectral images so that 24 macroscopically distinguishable colors (Table 1) can be created.

The amount of samples required for the test is 3.0 ml of heparin-treated blood in the case of chromosome testing for regular congenital abnormalities, and 1.0 ml of bone marrow fluid and 5.0 ml of blood in the case of blood disorders. Currently, no standardized method is available for describing chromosome karyotypes based on SKY analysis.

Table 1 Combination of fluorescent dyes (painting probes) in a chromosome analysis using SKY

Chromosome	Painting probes
1	BCD
2	E
3	ACDE
4	CD
5	ABDE
6	BCDE
7	BC
8	D
9	ADE
10	CE
11	ACD
12	BE
13	AD
14	B
15	ABC
16	BD
17	C
18	ABD
19	AC
20	A
21	DE
22	ABCE
X	AE
Y	CDE

A spectrum orange, *B* Texas red, *C* Cy5, *D* spectrum green, *E* Cy5.5

Characteristics of SKY in Clinical Application

When a chromosome in which the origin cannot be identified or the structural abnormality of a partial copy of a chromosome is observed with G-banding, the SKY technique makes it possible to recognize each chromosome with different color tones. Furthermore, when cells are cultured under conditions in which the image acquisition of cell division is difficult, SKY enables bleaching and staining of the specimen after the images of division have been verified.

SKY provides the advantage of easy visual interpretation when analyzing results, but it is not possible to evaluate structural abnormalities, such as inversion, deletion, insertion, and duplication in the same chromosome, because these are shown with the same color. Also, neither the Q-positive segment nor the satellite region of the long arm of the Y chromosome near the centromere can be detected. The resolution limit of detection is approximately 1–2 Mb, similar to conventional chromosome painting techniques, and minor structural abnormalities of less than 1 band cannot be detected. Therefore, in order to verify the site of chromosomal breakage, it is usually necessary to use SKY beforehand in combination with G-banding or

high-resolution chromosome banding, instead of using SKY alone to macroscopically observe the banding patterns.

Furthermore, SKY provides the following notable advantages. Conventionally, when a chromosome of unknown origin is noticed in a child suffering with some abnormality, a chromosome analysis is performed on both parents in order to make a definitive diagnosis of the chromosome in question. If a balanced structural abnormality is detected in the chromosome of either of the parents, then it is definitively diagnosed as the origin of such a structural abnormality. Conventionally, macroscopic evaluation would be performed based on the banding patterns, in case the informed consent for participation in the karyotype test cannot be obtained from the parents, and in the case of de novo translocation. In such cases, SKY has the advantage of being capable of readily clarifying the chromosome of unknown origin without performing karyotyping of the parents, and also can reveal if one of the parents is a carrier of a balanced structural abnormality. This advantage of SKY is very useful in the clinical practice of genetic counseling [9]. Refer to Table 2 for the indications of evaluation using SKY when structural chromosomal abnormalities are actually found via G-banding.

Case and Review

In this section, two cases in which SKY can be used are presented, and the benefits and limitations of this technique are discussed. We employed the application of 24-color SKY probes [Applied Spectral Imaging (ASI), Inc., ASI, Carlsbad, CA], skypaint™ hybridization and detection protocol, SRL Inc., Tokyo, Japan.

Case 1: Trisomy 11/22

The results of chromosome analysis on Trisomy 11/22 using SKY are shown in Fig. 1 [8, 9]. SKY was performed after an extra marker chromosome was detected in group G chromosomes via G-banding and the results showed the trisomy of chromosome 22. One of the extra chromosomes was distinguished by two colors, and it was deduced to be a derivative chromosome [der(22)], likely resulting from the reciprocal translocation in which the long arms of chromosome 11 (q23.3) and chromosome 22 (q11.2) were the breakpoints. The karyotype of this case is described as +der(22)t(11:22)(q23.3;q11.2). Therefore, SKY is one of the most effective approaches at present for the identification of an extra chromosome of unknown origin. With the use of SKY technique, it was possible to make a definitive diagnosis of trisomy 11/22 in the child without performing any chromosome testing on the parents, i.e., without examining the possibility of structural abnormalities that would have been inherited from either one of the parents. This is significant in the clinical practice of genetic counseling for parents to maintain their relationship.

Case 2: 13q-Syndrome

The results of the chromosome analysis of 13q-syndrome using SKY (Fig. 2) indicate structural abnormalities in chromosomes 2, 4, and 13 [12, 21]. For chromosomes 2 and 4, the reciprocal translocation t(2;4) with breakpoints on the long arm of chromosome 2 (q24.2) and the short arm of chromosome 4 (p14) can be readily distinguished. This t(2;4), however, may involve [inv(4)(p15.1p15.32)], which is a paracentric inversion with breakpoints at p15.1 and

Table 2 Usability when analyzing abnormalities that have been found via G-banding by using SKY

Result of G-banding	Karyotype	Supplementary note on SKY	Usability of SKY
Accessory chromosome	add	Identifies the derivative chromosome of an extra portion	[a]
Derivative chromosome	der	Identifies the related chromosomes	[a]
Insertion	ins	Identifies the derivative chromosome of insertion fragment	[a]
A complicated translocation		Identifies the related chromosomes	[a]
Genetic amplification	dimin/hsr	Identifies the derivative chromosome of homogeneous staining region	[a]
Duplication?	?dup	Identifies any duplication	[a]
Reciprocal translocation	t	Same analysis level of G-banding	[b]
Inversion	inv	Difficult to make an analysis that is better than G-banding	[c]
Deletion	del	Difficult to make an analysis that is better than G-banding	[c]
Numerical aberrations	+/−	Difficult to make an analysis that is better than G-banding	[c]
Unknown of derivative	mar	Identifies a derivative chromosome within the limitations of sensitivity	[c]
Cryptic translocation		Detects a derivative chromosome within the limitations of sensitivity	[c]

[a] The usability of SKY is considered to be high

[b] SKY can be used for analysis, but it cannot be expected to have better analysis results than those of G-banding

[c] Some cases cannot be detected using SKY

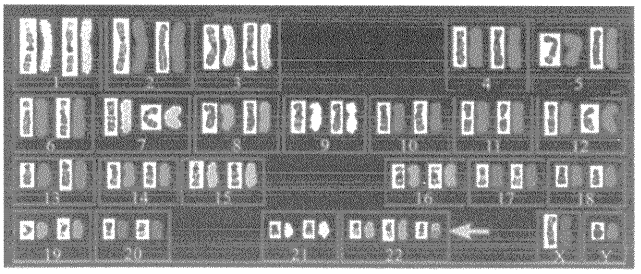

Fig. 1 Chromosome analysis on Trisomy 11/22 using SKY

p15.32 in the short arm part of chromosome 4 that has been translocated to chromosome 2, and this necessitates a verification via high-resolution chromosome banding. Inversions occurring in the same chromosome are not distinguished with color, so it is impossible to make a definitive diagnosis by using SKY. Thus in this case, testing of the parents' chromosomes via high-resolution chromosome banding is necessary for further detailed diagnosis.

For chromosome 13, it is possible to diagnose the occurrence of a deletion that is identified as 13q minus syndrome by using SKY only, but this does not reveal information about the breakpoints. By simultaneously combining this SKY-derived information with the banding patterns to be tested, it can be diagnosed as a paracentric deletion with breakpoints at q21.2 and q31.2. The karyotype of Case 2 is described as 46,XX, der(2)t(2:4)(q24.2;p14)inv(4) (p15.1p15.32), der(4)t(2;4), del(13)(q21.2q31.2) or 46,XX,t(2;4)(q24.2;p14), del(13)(q21.2q31.2). As stated above, it is difficult to make a definitive diagnosis from the results of a SKY analysis alone, and also one needs to be careful, because the conventional method of G-band staining cannot be used directly as a stand-alone substitute. Thus, more reliable interpretation and diagnosis can be made by combining the information from the two separate techniques, as neither of them can be used for unequivocal diagnosis.

When performing tests using SKY, it is necessary to understand the characteristics and the limitations of this analysis, and to combine the test results with those of G-band staining or high-resolution chromosome banding for a comprehensive karyotypic diagnosis.

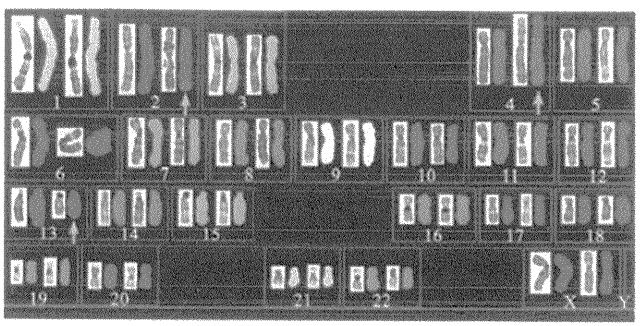

Fig. 2 Chromosome analysis of 13q-syndrome using SKY showing structural abnormalities in chromosomes 2, 4, and 13

Conclusion

With the introduction of SKY, a new technology of chromosome analysis, the accuracy of testing is improved and it now becomes possible to devise new clinical studies that previously had not been feasible with conventional testing methods. T-Band regions such as 1p, 11p15, 16p, 19p, 19q, and 22q are known as sites that are difficult to observe as bands of contrasting colors, even though it is believed that these regions contain many genes, according to conventional chromosome analysis. Furthermore, the macroscopic analysis of that band with the human eye involves a limitation in recognizing minor reciprocal translocations, and it is also possible that they may go unnoticed. Identification via SKY coloring has overcome the weakness of the conventional band pattern diagnosis method, and it is expected that other previously unrecognized specific chromosomal translocations are likely to be revealed with the widespread use of this technique.

Moreover, in recent years, spectral color banding has been developed as a technique that has overcome the limitations of SKY [22] and in this technique G-band differential staining is combined with the SKY coloring technology. Clinical use of this novel technique is expected to be widespread in the field of clinical genetics in the future and to make significant contributions. However, the cost of this technique still remains prohibitory. Considering these points, from the standpoint of genetic counseling, incorporation of SKY into G-band chromosome banding or high-resolution chromosome banding as needed would be the most practical technique of chromosome testing. In fact, when the structural abnormality of a chromosome of unknown origin is detected via G-banding, the combined use of SKY makes it possible to identify the origin without performing karyotyping of the parents, which could identify which parent is the carrier of the balanced structural abnormality. Therefore, in the clinical practice of genetic counseling, informed consent for a test of congenital chromosomal abnormalities can be readily obtained from the parents. Furthermore, an evaluation of the SKY results is made based on the colors that are displayed, so it is easy for a physician to explain the results to the parents of a patient. This advantage could potentially reduce the unnecessary psychological burden on parents with a child who demonstrates a structural abnormality in a chromosome.

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《特集Ⅰ》第29回日本思春期学会総会学術集会
シンポジウム2「男子思春期問題を考える－医学的立場からの検討－」

男性性器異常患児における思春期の問題点

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野々村克也

性分化異常症においては，出生直後の養育すべき社会的性の決定（gender assignment）とともに，決定した性に従った外陰形成術（genitoplasty）が必要である。男性性器異常患児では外陰形成術として尿道下裂形成術・精巣固定術・陰嚢形成術などが行われ，その目標とするところは女子外陰形成術も含め，1）決定された性に一致した外陰の外観の確保，2）尿失禁や尿路感染を伴わない正常な排尿機能の確保，3）成人に達した時の性機能・生殖機能の確保にある[1]。このような形成術は患児の生命維持に直接結び付かないことから，1960年代には学童期に入る前までに行うことが基準となっていた。その後1980年代には，小児に対する麻酔の発達や拡大鏡下のマイクロサージャリー技術の導入を背景に，患児の精神発達の観点より2歳を目処として形成術が行われるようになった。医療技術・環境の進歩につれ，形成術の早期施行が進む一方で，本人の意思確認をしない段階での不用意な手術と患者団体からの批判も登場してきた[2]。しかし，これら乳幼児期に行われた外陰形成術の長期成績に関する国内外の報告は少なく，適切な手術時期・術式に関してのエビデンスが求められている。今回，尿道下裂の手術を受けた患児が思春期に達した時の性機能，精神心理的問題に関しての調査結果を述べる。

尿道下裂は，男性への性分化異常の一徴候としてみられ，停留精巣に次いで多い外性器異常である。その状態を放置することにより外観の異常は勿論，患児の男性としての精神心理的発達にも影響を及ぼすことが懸念され，高度の下裂にあっては立位排尿や性行為が困難となる（図1）。したがって，尿道下裂形成術は外陰の正常な外観を得ると同時に，陰茎の屈曲を矯正し，外尿道口を陰茎先端に形成することを目的として，患児に性の

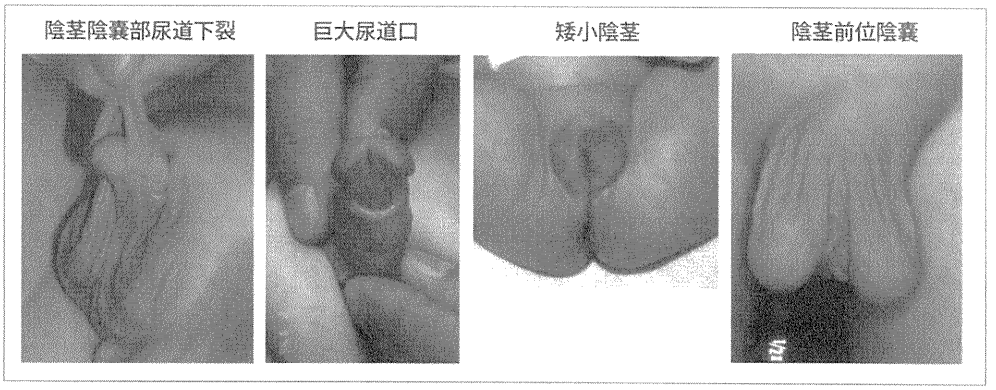

図1 尿道下裂の形態・種類

認識が芽生える以前に行われてきた。現在行われている術式において，その外観や立位排尿に関する短期成績に関して良好であるとする報告は枚挙に暇がない。一方，長期成績についての国内外の報告はわずかにすぎない。われわれが1980年代に尿道下裂形成術を行った患児の排尿・性機能についての長期成績を紹介する[3)11)]。

方　法

1983年以降に6歳以下で初回手術を受け，18歳以上に達した症例で接触可能な33例を下裂症例群とし，外陰の手術既往のない18歳以上の男性50例を対照群と比較検討した。

両群に自己記入式質問表に記入のうえ，郵送にて回収した。質問紙が返却された22例（遠位型9例，近位型11例，不明3例）について，38例の対照群と比較した。22例中16例はわれわれが開発した外尿道口周囲の包皮を尿道形成に用いる一期的尿道下裂形成術が行われている[5)]。1) 排尿症状に関する検討質問内容は①尿線の方向，②尿勢，③頻尿，④排尿姿勢，⑤尿の切れの五項目とした。2) 性機能に関する検討では陰茎の外観として，①大きさ，②瘢痕，③包茎，④屈曲，⑤外尿道口の位置，⑥全体の形，⑦亀頭の形などの項目について質問のうえ，①勃起能，②性欲，③勃起時陰茎の屈曲，④勃起時の問題の性行動に関する4項目を設定した。また，性行動の指標として，①自慰/性行為の初経験年齢，②射精/性交時についても問題とした。

結　果

1）排尿に関し，①尿線の方向，②尿勢，③頻尿，④排尿姿勢については下裂例と対照例に有意な差異はみられず，大多数例で排尿に支障がないと判断される（図2）。唯一，高度尿道下裂例で尿の切れが悪く，下着の汚れを防ぐために排尿後に尿道をしごくなどの操作を必要としていた（図3）。高度尿道下裂では形成新尿道が長く，通常尿道を包んでいる尿道海綿体や球海綿体筋の欠損などが関与していると考えられる。

2）性機能／性行動に関しては，外観上の問題点や満足度は全体として両群に差はみられなかっ

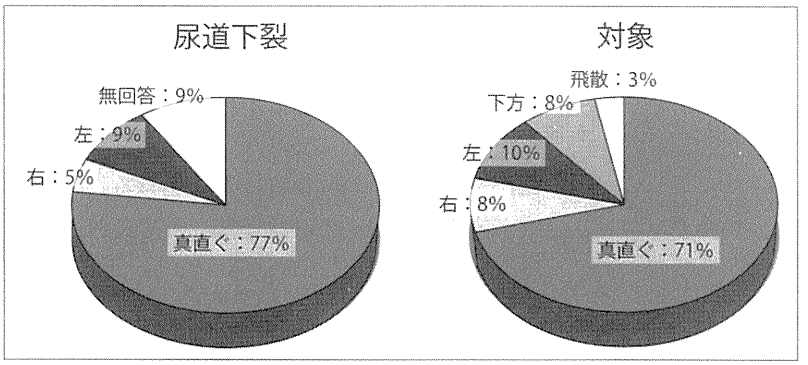

図2　尿道下裂形成術後長期観察
排尿状態

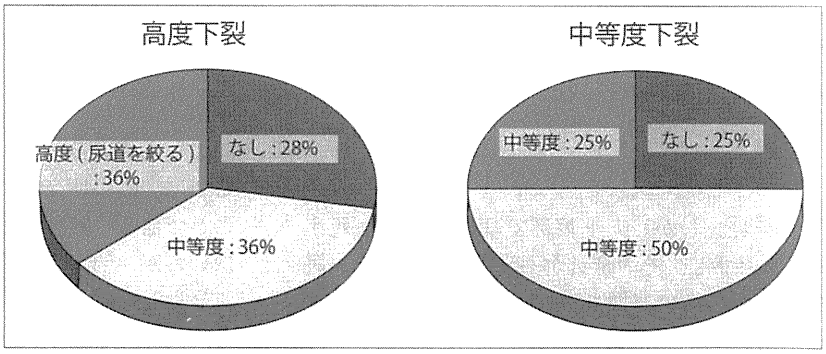

図3　尿道下裂形成術後長期観察
下裂の程度による排尿後の尿の切れ

表1　陰茎の外観についての満足度

	下裂群	対照群	
不満足(+)	40.9% (9/22)	34.2% (13/38)	N.S
矮小	100% (9/9)	69.2% (9/13)	
包茎	11.1% (1/9)	46.2% (6/13)	
屈曲	11.1% (1/9)	23.1% (3/13)	
尿道口の位置	11.1% (1/9)		
全体像	11.1% (1/9)	7.7% (1/13)	
亀頭の形	11.1% (1/9)		
瘢痕		15.4% (2/13)	
色調		7.7 % (1/13)	
陰茎部陰毛		7.7 % (1/13)	

表2　自己陰茎の外観について

	下裂群	対照群	
	63.3% (14/22)	42.1% (16/38)	N.S
矮小	71.4% (10/14)	37.5% (6/16)	
瘢痕	21.4% (3/14)	12.5% (2/16)	
包茎	14.3% (2/14)	50.0% (8/16)	
屈曲	14.3% (2/14)	12.5% (2/16)	
割礼後の状態	7.1% (1/14)		
外尿道口の位置	7.1% (1/14)		
全体像	7.1% (1/14)		
色調	7.1% (1/14)		
亀頭の形		12.5% (2/16)	
過大		6.3% (1/16)	
その他		12.5% (2/16)	

表3　自慰/性経験

	下裂群	対照群
[自慰]		
経験あり	100% (21/21)	97.4% (37/38)
初経験年齢 (平均±SD)	13.4 ± 1.4	13.0 ± 1.9
頻度（回/週) (中央値±SD)	2.5 ± 1.5	2.5 ± 2.2
[性経験]		
経験あり	52.4% (11/21)	55.3 % (21/38)
初経験年齢 (平均±SD)	16.6 ± 1.8	17.3 ± 1.3
過去のパートナー数 (中央値±SD)	2.0 ± 2.2	2.5 ± 3.3
現在性パートナー(+)	36.4% (4/11)	35.0% (7/20)

た（表1)。しかし，下裂群では70％以上が短小であると感じ，その全員が不満足としていた（表2)。両群の性的経験をみると，自慰の初経験年齢や頻度に差はみられず，はじめての性経験年齢や性パートナーの有無に関してもまったく差がみられなかった（表3)。実際の性行為では，射精後勃起能などは対照群と差がみなれなかったが，陰茎が小さいということが一貫して性行為・性行動に影響を与えていた。

コメント

男性化外陰形成術には，主として停留精巣に対する精巣固定術と尿道下裂に対する形成術がある。その長期成績に関しては精巣固定術においては妊孕性，尿道下裂においては排尿機能・性機能の獲得に主たるエンドポイントがある。停留精巣は乳児期の組織像や成人に達した時の精液所見より，生後6ヵ月から2歳未満に手術を行うのが現在妥当とされている[6]。また，尿道下裂の形成術も乳幼児に対する麻酔技術の進歩や拡大鏡・マイクロサージャリー技術の導入により1－2歳での手術がルーチンに行われるようになってきた。

排尿機能に関しては，尿流量測定・残尿測定などの手法により客観的評価が行われている。手術術式により成績が異なるが，10－20％で閉塞パターンが示され，アンケートからもわかるように日常生活に支障はないものの長期の機能評価が必要である[7]。従来の報告で多かった尿の飛散に関してはアンケート上問題となっておらず，1980年代に行われるようになってきた亀頭外尿道口形成術が結果に反映していると考えられる。高度尿道下裂で多い尿の切れの悪さは，尿道海綿体の支持の形成尿道に尿が残ることによるもので，現在の陰茎皮膚を用いた尿道形成術では限界がある。

性機能・性行動に関しては，勃起能・性欲・性体験などは対照群と差がみられず，心理学的な面から幼児期手術が性活動に及ぼす影響を小さくするとの従来の報告を支持する。しかし，尿の切れの悪さと同様のことが射精時に生じ，一定数で問題となっている。最も大きな問題点は，外観上あるいは実際の性交時に陰茎が小さいと感じていることである。外科的治療の範囲を一定程度超えてはいるが，明らかな矮小陰茎合併例では長期予後を見通した内分泌学的治療が模索されるべきである。従来，尿道下裂患児が成人に達した後の内分

泌学的検討は今まで散発的に少数例の報告があるにすぎない[8][9]。遠位下裂型で20%，近位下裂では停留精巣合併の有無にも関連するが30～50%近くに下垂体－性腺系の異常がみられるとされる。われわれの最近の検討でも同様で，乳幼児期に手術を受けた尿道下裂症例において停留精巣合併例も含め，高率に下垂体－性腺機能の異常がみられる[10]。内訳としては，hypergonadotropic /hypogonadotropic hypogonadism, androgen resistance 症候群などが含まれる。これら内分泌学的異常の有無にかかわらず，症例一人ひとりの経過観察は大切であるが，現実には親の転居などフォローを失う要素が多い。手術時の両親に対するインフォーム，思春期前後のコンサルト，学生から成人/社会人への移行期のコンサルトなどを体制化することが理想であるが，泌尿器科単独では無理があり，小児科・内科，精神科・心理士，教師などを巻き込んだ展開が必要である。

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尿道下裂症例の思春期を中心とした成人患者における下垂体−性腺系

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日本小児泌尿器科学会
Japanese Society of Pediatric Urology

学会賞受賞論文

尿道下裂症例の思春期を中心とした成人患者における下垂体−性腺系

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要　旨

【目的】尿道下裂の原因については様々な報告がなされているが、その一つに内分泌学的異常がある。過去の報告において幼少期の内分泌学的異常の報告は散見されるものの、下垂体−性腺系が活性化される思春期にいかなる影響があるのかについての報告はごく僅かである。今回の検討では、尿道下裂の形態と思春期の下垂体−性腺系について検討した。

【対象・方法】当科で手術を行い、15歳以上で評価を行った43例を対象とし、尿道下裂の程度・合併する精巣疾患と、LH・FSH・テストステロン及び精巣容積の関係を検討した。

【結果】43例中14例が遠位型尿道下裂であり、29例が近位型であった。近位型のうち8例に停留精巣の既往歴があった。これらの症例を遠位型(14例)・停留精巣既往のない近位型(21例)、停留精巣既往のある近位型(8例)に分けて検討を行った。遠位型ではhypogonadotropic hypogonadism、低テストステロン血症、低LH血症、hypergonadotropic hypogonadismを各1例に認めた。停留精巣既往のない近位型では低テストステロン血症1例、hypergonadotropic hypogonadism1例、アンドロゲン不応症1例がみられた。停留精巣既往のある近位型ではhypergonadotropic hypogonadism、高LH血症を各2例に認めた。高FSH血症を伴う萎縮精巣(10ml未満)は7例に認められ、遠位型1例、停留精巣既往のない近位型2例、停留精巣既往のある近位型4例であった。

【結論】思春期における内分泌異常は遠位型・近位型ともに存在し、停留精巣の既往ない症例でも認められた。そのうち、停留精巣既往のある近位型尿道下裂群では造精機能障害が疑われる症例の割合が高かった。

キーワード：尿道下裂、停留精巣、下垂体−性腺系

緒　言

尿道下裂は外尿道口の位置異常、陰茎背側の余剰包皮、陰茎の腹側への屈曲(索変形)を特徴とする先天性疾患である。その病因については、未だ不明な点が多いが内分泌学的異常などを含む多因子的なものが考えられている[1,2]。

男児の尿道が形成される過程においてアンドロゲンが作用していることが広く知られており、近年では内分泌かく乱物質の影響により尿道下裂の発生頻度が増加している可能性が示唆されている。しかしながら尿道下裂に罹患した患児において、下垂体−性腺系が活性化する思春期の内分泌環境に関する報告はごく僅かである。今回の検討では、尿道下裂の形態と思春期の下垂体−性腺系について検討を行った。

対象・方法

当科で加療した尿道下裂症例のうち15歳以上で内分泌検査を行った43例(15.1歳−22.8歳：平均17.6歳)の検討を行った。これら症例における尿道下裂の程度・合併する精巣疾患をレトロスペクティブに検討した。

下垂体−性腺系については、LH・FSH・テストステロンを測定した(測定方法は、LH、FSHは化学発光免疫測定法(CLIA法)、テストステロンは電気化学発光免疫測定法(ECLIA法)を用いた。基準値はLH：1.7-11.2 mIU/ml、FSH：2.1-18.6 mIU/mlテストステロン：262-960 ng/dl)。さらに、Prader's orchidometerを用いて精巣容積の測定を行い、大きい側の精巣が10ml未満の場合を萎縮ありと定義し検討を行った。

結　果

43例の患者背景は遠位型14例、近位型29例に分けられた。近位型のうち8例で停留精巣に対する手術歴があった。経過観察中に遠位型の1例で精索静脈瘤を、近位型の2例で精索捻転を認め、いずれも停留精巣の既往のない症例であった。全例とも外陰はTanner Stage 4-5度であった。

遠位型(14例)、停留精巣既往のない近位型(21例)、停留精巣既往のある近位型(8例)それぞれにおける血中LHとテストステロンの関係の結果は、遠位型ではhypogonadotropic hypogonadism、低テストステロン血症、低LH血症、hypergonadotropic hypogonadismを各1例(計4例；29%)に認めた(図1)。停留精巣既往のない近位型では低テストステロン血症1例、hypergonadotropichypogonadism1例、アンドロゲン不応症1例(計3例；14%)がみられた(図2)。停留精巣既往のある近位型ではhypergonadotropic hypogonadism、高LH血症を各2例(計4例；50%)に認めた(図3)。

高FSH血症を伴う萎縮精巣は7例に認められた。各群別の内訳は、遠位型1例(7%)、停留精巣既往のない近位型2例(10%)、停留精巣既往のある近位型4例(50%)であった(図

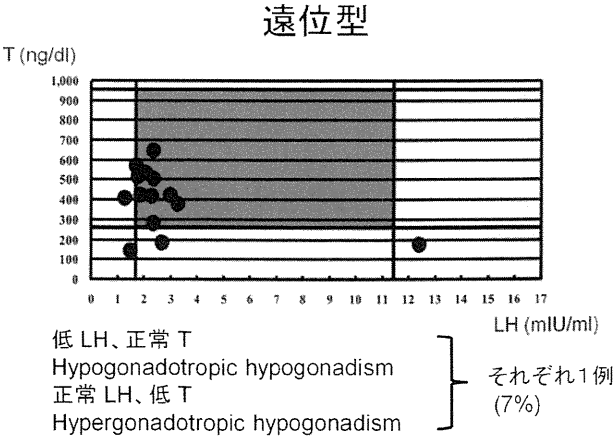

図1：遠位型尿道下裂患者における血中LHとテストステロン(T)の関係。14患者のうち低LH血症、hypogonadotropic hypogonadism、低テストステロン血症、低LH血症、hypergonadotropic hypogonadismを各1例(計4例；29%)に認める。

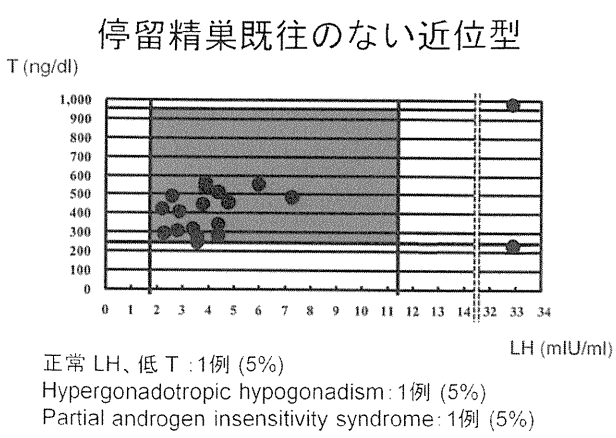

図2：停留精巣既往歴のない近型尿道下裂患者における血中LHとテストステロン(T)の関係。21患者のうち、低テストステロン血症1例、hypergonadotropic hypogonadism 1例、アンドロゲン不応症1例(計3例；14%)に認める。

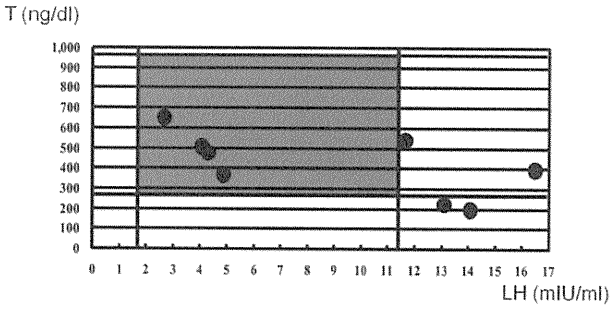

図3：停留精巣既往歴のある近型尿道下裂患者における血中LHとテストステロン(T)の関係。8例中、hypergonadotropic hypogonadism、高LH血症を各2例(計4例；50%)に認める。

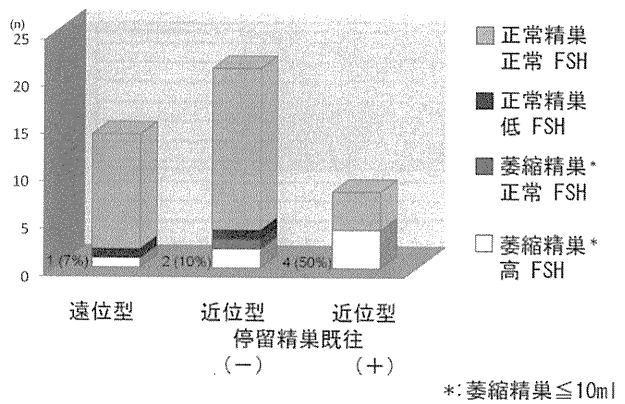

図4：精巣容量と血清FSHの関係。高FSH血症を伴う委縮精巣(10ml未満)は7例に認められ、遠位型で1例(7%)、停留精巣既往のない近位型で2例(10%)、停留精巣既往のある近位型で4例(50%)に認めた。

4)。

考　　察

尿道下裂の発生には様々な要因が関与しているが、その一つに内因性の内分泌異常が知られている。従来から高度の尿道下裂症例や停留精巣・矮小陰茎などを伴う症例の一部には内分泌学的異常を有する症例が存在することが知られていたが、これまで幼少期の内分泌動態に関してはいくつかの報告あるものの[3]、思春期以降の報告はごく僅かであった[4),5)]。本検討の結果が示すように、尿道下裂症例の一部には思春期においても内分泌学的異常を呈する症例が存在する。その発生頻度は、フォローアップの問題から今回の検討のみでは明らかではないものの、少なくとも近位型・遠位型ともに異常を認める症例が存在することから、術前あるいは術中所見のみで内分泌学的な長期的予後を予想することは困難であると考えられた。

また、現在までに思春期における尿道下裂と造精機能の関係は十分に検討されていない。これまでに不妊症男性患者と精巣のサイズの間には有意な関係があることは示されている[6-8)]。今回の検討では総精巣容量が20ml以下の場合に造精機能障害との関連を認めたという過去の報告に準じて[6)]最大精巣容積が10ml以下の場合を萎縮精巣と定義し、さらにはその役割には不明な部分が多い部分がものの[9)]高FSH血症は男性不妊のリスクファクターであることも報告されている[10,11)]ことから、萎縮精巣を伴う高FSH血症症例を造成機能障害の疑われる群と考え、その頻度を検討した。その結果、萎縮精巣を伴う高FSH血症症例は全体の16%にみられ、これは停留精巣歴のある近位型尿道下裂患者の50%にあたる(図4)。症例が少なく統計学的な検討は行っていないが、これは過去の報告における、他の尿路奇形を合併する尿道下裂症例に精子形成不全症例が多く存在することに一致する[12,13)]。しかしながら、停留精巣歴のない35症例のうち3例(9%)にも高FSH血症を認めており、これは過去の報告における正常コントロール群(健常者群)での高FSH血症の発現率2%に比べて高い[14)]。この結果から、尿道下裂症例に造精機能異常や父性獲得に障害が疑われる症例が存在する可能性が高いことが示唆される。

尿道下裂治療の目的は外観の正常化とともに良好な排尿が行える尿道を形成すること、および将来の性交渉に問題のない陰茎を形成し、最終的に父性を獲得することにある。過去に我々が報告してきた様に[15)]尿道下裂術後の長期予後はおおむね良好であり、手術の目的は多くの患者で達成されていると考えられる。その反面、幼少期に外科的治療を終了した患児の一部は、思春期以降になって顕在化する問題点を有することも明らかになってきている。その問題点は手術手技に起因する(尿の切れ・射精時のmilkingなど)と考えられるものもあれば、尿道下裂と同じ原因によると考えられるもの(陰茎のサイズや内分泌学的問題)も存在する。尿道下裂は小児泌尿器科領域では比較的頻度の高い疾患であり、幼少期に外科的治療が完了することが多く長期間のフォローは困難な場合も少なくない。しかしながら、治療を行う際には上述のような長期的な問題点を医療者側が理解し、患児の家族が抱える長期的な不安に対して十分な説明を行うとともに、少なくとも思春期までのフォローアップが必要なことを説明すべきである。

本研究において、レトロスペクティブな検討であるために精液検査を行っていない点は今後の検討課題と考えられる。さらに、停留精巣のない近位型の症例の中にアンドロゲン不応症を示唆する症例を確認したが、今回は遺伝子解析等を施行できておらずホルモン検査結果のみからの診断としている。さらに、その他の症例がアンドロゲン不応症でないかの検索も行えていない点は本検討の限界であり、同様に今後の検討課題と考えられた。

近位型のみでなく遠位型において、さらには停留精巣の既往がなくてもホルモン異常となる可能性があることから、尿道下裂症例は長期にわたるフォローが必要であると考えられる。

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