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Analysis of Clinical Characteristics of 4 Patients with Super-female Syndrome

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Abstract: *In order to explore the clinical characteristics of children with supergynous syndrome, We retrospectively analyzed the clinical data of 4 patients with supergynous syndrome, including karyotype, height, hormone level and other related data, and their clinical characteristics were discussed in combination with literature review. Two patients with 45, X/47, XXX mosaic type all had different degrees of short stature, and 1 case was complicated with partial growth hormone deficiency; 2 cases of non-chimeric type 47, XXX patients did not appear short stature, and among non-chimeric type patients One case was within the range of the normal population, and the other had a tall stature, and one of them showed symptoms of more typical superfemale syndrome, such as mild mental retardation. The sex hormone levels of Case 1, Case 2, and Case 4 were in line with the age characteristics of the children, and the sex hormone examination of Case 3 was not perfect. None of the 4 patients had abnormal gonadal development through physical examination and imaging studies, and the development of the uterus was in line with the age characteristics of the children. Symptoms of patients with superfemale syndrome are diverse and lack typical features. The clinical symptoms of patients with 45, X mosaicism are similar to those of Turner syndrome.*

Keywords: *G-banding karyotype analysis; Super-female syndrome; Mosaic type*

1. Introduction

Hyperfemale syndrome is a kind of chromosome aneuploid disease. Most of the patients have normal phenotype, which is not significantly different from that of normal women. Sometimes it may be accompanied by defects such as wide eye distance, wide breast distance, and a few have slight developmental delay. The possibility of learning difficulties is slightly higher than that of ordinary people, language skills are slightly poor, and some patients show mental retardation. Most patients with super-female syndrome have normal sexual development and fertility, and patients may have reduced menstruation, secondary amenorrhea or premature ovarian failure, and a few are accompanied by abnormal structure of urinary and reproductive system [1]. The disease was first reported by Jacobs and others in 1959. A 35-year-old woman with 47，XXX karyotype and normal intelligence was found in the case of secondary amenorrhea for 6 years [2]. Since then, cases have been reported at home and abroad. Through consulting the literature, it can be known that the cause of super-female syndrome is that the patients with the disease have one or more extra X chromosomes than the normal women, and the normal women are in the 46,XX karyotype. However, the X chromosome has a homologous region with the Y chromosome, known as the pseudo-autosomal region (pseudoautosomal regions, PAR), in which genes are not inactivated and remain expressed. The region carries asthma, mental disorders, leukemia, and SHOX genes associated with dwarfism. In addition, about 5-10% of the genes on the X chromosome continue to be expressed. Therefore, it can be speculated that the clinical characteristics of children with super-female syndrome may be related to the abnormal expression of the above genes due to the existence of multiple X chromosomes in the patients [3]. The most common karyotype of super-female syndrome is 47, XXX, but there are still about 10% cases of chimerism, including 45, X/47, XXX,46, XX/, 47, XXX etc [1]. According to the reports of cases at home and abroad, mosaic patients have different clinical characteristics. 47, XXX/47, XX, +21, patients and 21, trisomy syndrome patients have similar faces, while 47, XXX/48, XXX, +8 patients have shown Behchet's syndrome [4,5]. Patients with 45/X chimerism have similar clinical manifestations to Turner syndrome [6]. It is reported abroad that the incidence of 47 chromosome XXX in neonatal screening is 1/1000, and the diagnosis rate is 10% [7]. Similarly, according to recent data from the Danish Cellular Genetics Registry, the incidence of karyotype 47, XXX in women is about 11 hundred thousand, with a diagnosis rate of 13% [8]. In China, Huang Xiaoli, Sun Lizhou and

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others used non-invasive prenatal detection technique to screen 19327 fetal sex chromosomes and found that the karyotype was 47, and the detection rate of XXX was 0.06% [9]. Due to the diversity of clinical symptoms of the disease, there are no criteria for diagnosing the disease according to the symptoms at home and abroad. This paper introduces 4 patients with superfemale syndrome detected by G-banding karyotype analysis of peripheral blood cells, to further understand the cytogenetic characteristics and clinical manifestations, and to provide help for clinical diagnosis and treatment.

2. Means of inspection

Karyotype analysis of peripheral blood is the most standard examination for diagnosis, as shown in Figure 1. Prenatal amniocentesis or CNV-seq, FISH and other techniques can also diagnose hyperfemale syndrome. At least 50 cells were analyzed to evaluate whether they were chimera [3]. Genetic counseling was conducted through medical history inquiry and physical examination. The peripheral blood cells of suspicious subjects were analyzed by cell culture, fixation, chromosome preparation, G-banding, photography and oil microscope analysis, and the chromosome karyotype was analyzed according to the International Nomenclature system of Human Cytology (ISCN 1978), as shown in Figure 2.

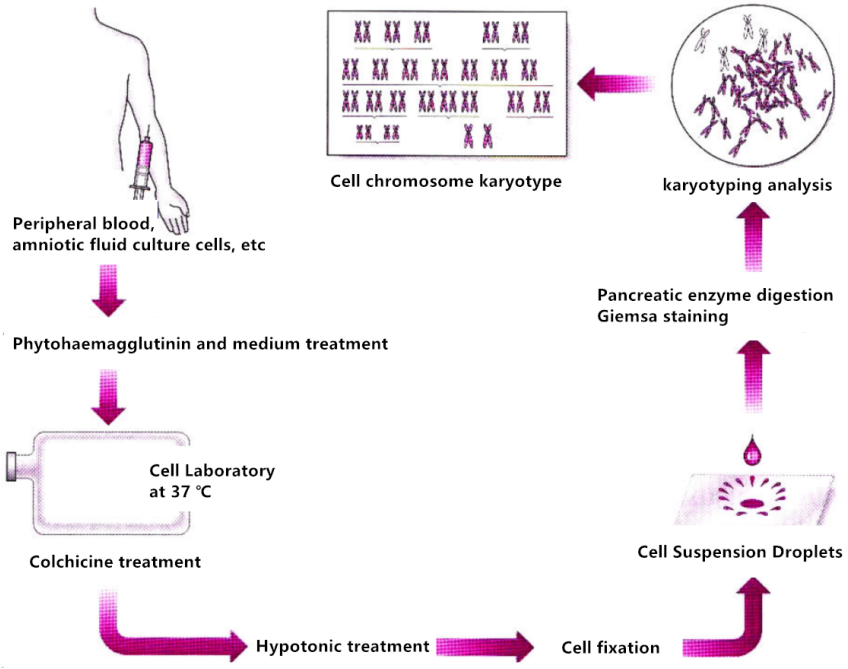

Figure 1: Karyotype analysis of peripheral blood

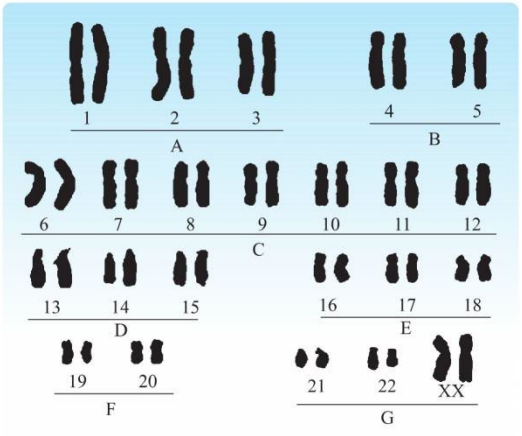

Figure 2: Normal human karyotype

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3. Case data

Case 1, female, 12 years old and 1 month old, rising and growing too fast in the past 2 years, the annual growth rate was more than 10cm/ year, the mental development was slightly lagging behind, the exercise milestone was later than that of the same age, it was easy to fall when walking at 1 year old, and steady at 2 years old. The child is G2P2, full-term infant, no history of anoxia during delivery, birth length 58cm, birth weight: 2.8Kg, father's height: 178cm, mother's height 155cm. Physical examination: W:50.5kg (P75-90), H:176.5cm (> P97, 3.68S) upper part 72.5cm, lower part 104cm, upper/ower quantity 0.69, finger spacing 177cm. The lumbar vertebrae bent to the right, the limbs and toes were slender, the muscle tension of the extremities was acceptable, the thumb sign and wrist sign were positive, and the knee varus was positive. Tall stature, thin figure, no special face, heart, abdominal physical examination is not special. 10-year-old menstruation, regular cycle. Stage IV of Tanner. Evaluation of endocrine-related tests: fasting blood glucose, fasting insulin, free thyroid function, adrenocortical function and growth factors were almost normal. Sex hormone:FSH:4.39IU/L, LH:3IU/L, E2:45pg/ml. Ultrasound of uterus and adnexa: the size of uterus was 47×32×49mm, the thickness of endometrium was about 8mm, the size of right ovary was 28×21×19mm, and the size of left ovary was28×20×16mm. The bone age was estimated to be 12.2 years old by left hand X-ray positive radiography (Greulich-Pyle). (Figure 3, Patient 1). Lower limb plain film, knee, hip joint plain film was not abnormal, abdominal, adrenal, cardiac ultrasound was not significantly abnormal, pituitary magnetic resonance imaging was not abnormal tomorrow. The karyotype analysis of peripheral blood cells by G-banding method showed 47, XXX. Parents are not related to each other and deny family history.

Case 2, female, 4 years old and 10 months old, consciously grew slowly for more than 2 years, the annual growth rate was unknown, and there was no obvious lag in motor and intellectual development compared with children of the same age. Department of G1P1, full-term infants, no history of postpartum hypoxia asphyxia. Birth length 49cm, birth weight 2.5Kg, father height:172cm, mother height:163 cm, physical examination: W:16.5kg (P10-25) H:102.8cm (P3-10). Upper part: 53cm, lower part: 49.8cm, upper part/lower part: 1.06:1. The body is symmetrical, no special face, no cubitus valgus, no abnormal performance. External genitalia of girls, Tanner stage I. Evaluation of endocrine-related tests: fasting blood glucose, blood ammonia, fasting insulin, free thyroid function, adrenocortical function and growth factors were almost normal. Sex hormone:FSH:2.49IU/L, LH:0.06U/L, E2: < 10pg/ml. Growth hormone stimulation test showedthat the peak value of GH was 11.9ng/ml. Ultrasound of uterus and adnexa: the size of uterus was13×6.4×9mm, the size of endometrium was not shown. The size of right ovary was21×11×7mm and that of left ovary was20×14×8mm. Bone age: BA-CA=2.1-4.8=-2.7(Greulich-Pyle). (Figure 3, Patient 2). No obvious abnormality was found in abdominal ultrasound andnuclear magnetic resonance of pituitary. The positive and lateral position of lumbosacral vertebrae showed that the curvature of lumbosacral vertebrae became slightly straight. The anterior part of lumbar 2-5 vertebral body became sharp, and the anterior partof lumbar 2 vertebral body was irregular. The karyotype analysis of peripheral blood cells by G-banding method showed 47, XXX. Parents are not related to each other anddeny family history.

Case 3, female, 5 years and 5 months, had an annual growth rate of less than 5cmdue to short stature since childhood, no chronic headache, nausea, vomiting, ignorance and blurring, and no obvious lag in motor and intellectual development compared withchildren of the same age. Department of G2P2, full-term, birth length unknown, birthweight 3kg. W: 17kg (P10-25) H:99cm (6cm under P3) BMI:17.34kg/m2 3.26SD (P75-90). Upper part: 56.5cm, lower part: 42.5cm, upper part/lower part: 1.32. The patient was short in stature, the lower jaw was sharp and showed "inverted triangle", the parents had no similar facial shape, the right chest was higher than the left chest, and there was no abnormal appearance. There is no special physical examination of heart, lungs and abdomen. External genitalia of girls, Tanner stage I. Evaluation of endocrine-related tests: fasting blood glucose, fasting insulin, free thyroid function, growth factor, adrenocortical function rhythm were about normal. All the sex hormones were not tested. The perfect growth hormone stimulation test showed that the highest value of growth hormone was 2.33ng/ml and the bone age was 6.9 years old. (Greulich-Pyle). (Figure 3, Patient 3). No obvious abnormality was found in abdominal ultrasound, pituitary nuclear magnetic resonance and lumbosacral positive and lateral position. Ultrasound of uterus and adnexa:the size of uterus was16×6.4×9mm, the size of endometrium was not shown. The size of right ovary was21×11×9mm, and that of left ovary was20×14×8mm. The karyotype analysis of peripheral blood cells by G-banding method showed that45, X/47, XXX. Parents are not related to each other and deny family history.

Case 4, female, age 5 years and 11 months, was found to be short for 3 years, with an annual growth rate of less than 5cm, no mental retardation and normal psychomotordevelopment. Aortic stenosis operation was performed 2 months after birth. Department of G1P1, full-term, birth length 50cm, birth

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weight 3kg. W:17.5kg (P10-25) H:108.4cm (P3) BMI:15.0kg/m2 (P75-90). Upper part: 55cm, lower part: 53cm, upper part/lower part: 1.04. The stature is short, the neck web (+), the milk distance is wide, other no abnormal performance. There is no special physical examination of heart, lungs and abdomen. External genitalia of girls, Tanner stage I. Evaluation of endocrine-relatedtests: fasting blood glucose, fasting insulin, free thyroid function, growth factor, adrenocortical function rhythm were about normal. Sex hormone: FSH:6.3IU/L, LH:0.15U/L, E2: < 10pg/ml. The growth hormone stimulation test showed that the highest value ofgrowth hormone was 6.48ng/ml and the bone age was 4.6years old. (Greulich-Pyle). Ultrasound of uterus and adnexa: infantile uterus (consistent with the age ofthe child), no obvious abnormality was found in both ovaries. The karyotype analysisof peripheral blood cells by G-banding method showed that 45, X/. Parents are not related to each other and deny family history.

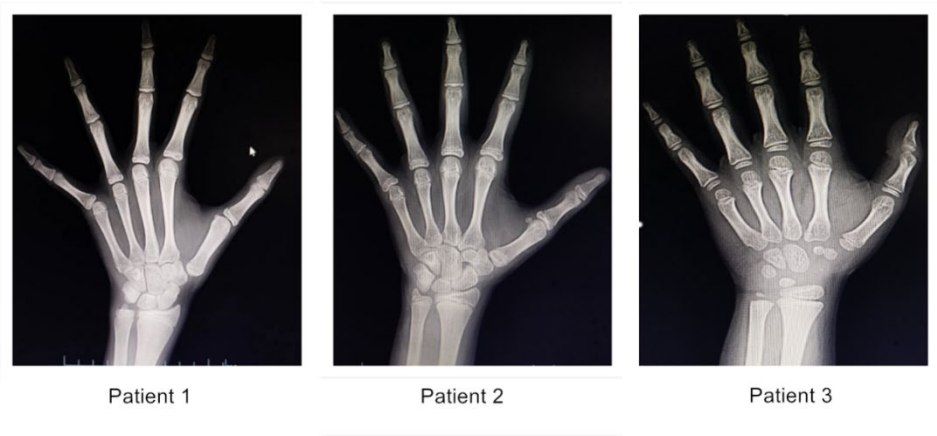

Figure 3: Imaging materials of X scan (The bone age of patient 4 was perfected in the outside hospital, and there was no imaging)

4. Phenotype of physical signs of 4 patients

Two patients were clinically short in varying degrees, and the other two patients were not short in height. The karyotypes of 2 patients with short stature were all chimerism, accompanied by mild Turner syndrome-like signs, such as sharp mandible, "inverted triangle", right thorax higher than left thorax, neck web, wide milky distance, etc., but the phenotype was lighter than that of typical Turner syndrome. One of the patients with non-chimerism showed typical super-female syndrome, such as tall stature, backward growth and development milestone and mild mental retardation. None of the 4 patients showed gonadal dysplasia. (Table 1)

In terms of hormone level, LH:3U/L (> 0.2U/L) in case 1 and 45pg in E2Vue, which indicated spontaneous puberty of the patient. The LH:0.06U/L of case 2 (< 0.2U/L), E2: <10pg, LH:0.15 of case 4 (< 0.2U/L), E2: <10pg, indicated that the patient was underdeveloped and conformed to the patient's age. The levels of sex hormones in case 1 were consistent with the characteristics of age. The size of uterus in 4 patients accorded with the age characteristics of children. Case 1 was not short and the GH challenge test was not perfect. The perfect GH challenge test of 2 patients with chimerism showed that the maximum value of GH was lower than normal. (Table 2)

Table 1: The physical sign phenotypes of 4 patients

number	age	Karyotype	H	Gonadal development	Special physical signs	Intelligence/ cognition
1	12	47, XXX	>P97	normal	Thumb sign, wrist sign, knee varus	Intellectual and cognitive retardation
2	4	47, XXX	P3-P10	normal	normal	normal
3	5	45, X/47, XXX	<P3	normal	The lower jaw is "inverted triangle".	normal
4	5	45, X/47, XXX	<P3	normal	Neck web (+), wide breast distance	normal

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Table 2: The imaging and laboratory examination of 4 patients

number	FSH(U/L)	LH(U/L)	E2(pg/mL)	GH(max)(ng/mL)	Uterine ultrasound	Bone age
1	4.39	3	45	-	Uterine and ovarian development	13.6
2	2.49	0.06	<10	11.9	Infantile uterus	2.1
3	-	-	-	2.3	Infantile uterus	6.9
4	6.3	0.15	<10	6.4	Infantile uterus	4.6

5. Discussions

The clinical manifestations of patients with super-female syndrome are different and the symptoms are relatively mild, and the rate of clinical diagnosis is not high [1]. There were differences in clinical manifestations among patients of different ages, and there was no significant difference in body length and weight between newborn infants with super-female syndrome and normal infants. Children with low muscle tone in infancy are prone to language and motor retardation, and their height increases rapidly at the age of 4-8 years old [10]. In addition to having a tall stature, patients before puberty may also show folding of epicanthus, increased pupil spacing, flat foot, funnel chest and so on. The speech IQ and behavioral IQ of the patients with super-female syndrome were relatively low, and most of the comprehensive IQ were at the average or above level. They are more likely to develop attention deficit, hyperactivity disorder and autism spectrum disorders as they grow up. Puberty and post-puberty children may have tall stature, in addition to special faces, there may be delayed development of secondary sexual characteristics, menstrual disorders, premature ovarian failure and so on. [11]. Studies have shown that [2] with the increase in the number of X chromosomes, the risk of abnormal appearance, growth retardation, mental retardation, loss of ovarian function and clinical diseases increases. The occurrence of 47.XXX syndrome is an inseparable event with randomness. 90% of the inseparable events are maternal. And the mother's age is an important risk factor, which is similar to other autosomal trisomy syndrome. And as the mother gets older, the risk of the disease increases. Other related studies have suggested that the main reasons for the appearance of extra X chromosomes are: 1. During the first meiosis, X chromosome non-disjunction accounted for about 70%, 2. During the second meiosis, non-separation accounted for about 20%, 3. There are also about 10% of non-dissociation events that occur after the formation of fertilized eggs, resulting in cell mitosis error formation, which is the mechanism of chimeric XXX syndrome, such as 45,X/47,XXX. There was no significant correlation between the incidence of these chimeric XXX syndrome and maternal age [12].

Case 1 and case 2 are non-chimeric patients, and their stature is not short, among which case 1 shows more typical manifestations, such as high stature, mildly backward intelligence, backward development milestone and so on. According to related research, in normal 46 X women, one of the X chromosomes is selectively inactivated, but there are specific fragments (PAR1 and PAR2) on the X chromosome that are not inactivated, and the study found that about 5% of 10% of the X chromosomes outside the PAR region also escaped X inactivation, in which ZNF67 may be related to low IQ and cognitive impairment [13]. Therefore, it is speculated that the cause of mild mental retardation in this patient may be related to the excessive number of X chromosome and the decrease of methylation of ZNF63 and other genes. Case 2, bone age lagging behind more, lagging behind the age of 2.7years, foreign scholars Stagi and other studies found that patients with super-female syndrome may have impaired bone mineral status and bone metabolism, the reasons for more bone age lag may be related toabnormal bone metabolism [14]. Existing clinical studies have shown that 47, XXX is the most common clinical karyotype, but 10% of patients still exist in the form of chimera. The patients with chimeric karyotype had relatively different clinical features. It was reported that the appearance of 47, XXX/47, XX, +21, patient was similar to that of trisomy 21. The appearance of the patients with chimerism with 45, X cell line was similar to that of Turner syndrome [15].

Case 3 and case 4 were chimeric patients, all of them were short and their height was less than-2SD, and they all had Turner's syndrome-like manifestations in different degrees: case 3 had a small mandible, case 4 had a cervical web (+) and a wide milky distance. However, compared with the patients with typical Turner syndrome, it is concluded that the overexpression of genes in 47, XXX cell line makes up for the insufficient expression of some genes in 45, X cell line to some extent, which makes the symptoms milder than that of typical Turner's syndrome [16]. In case 3, the highest value of growth hormone in

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perfect growth hormone stimulation test was 2.3 ng/mL, the levelof growth hormone was normal, and there was no obvious lag in bone age, so it is necessary to consider the possibility of false positive in growth hormone stimulation test. Case 4 showed that the highest value of growth hormone secondary stimulation test was 6.48ng/mL, the annual growth rate was less than 5cm, and the bone age was lagging behind, so partial growth hormone deficiency was diagnosed. Frederiksen et al found that mutations in SHOX gene may affect bone structure and bone mineral density, and related studies have shown that underexpression of SHOX will lead to short stature [17]. Therefore, case 3 and case 4 consider that the cause of slow growth may also be related to the lack of haploid of SHOX gene. Compared with the typical Turner syndrome, the X chromosome is directly related to the genes related to body growth and gonadal development, but the clinical symptoms of the chimera are relatively mild. It has been reported that most of the 45,X/47,XXX chimeric children can reach normal height without rhGH treatment, and most of them have spontaneous menarche. The main treatment for 45,X/47,XXX chimeric patients is dwarfism and gonadal dysgenesis, but because the clinical symptoms are relatively mild, the proportion of patients who need rhGH and sex hormone replacement therapy is lower than that of children with typical Turner syndrome, and there is no difference in treatment plan. However, during the follow-up, we should pay attention to the menstrual cycle and guard against the occurrence of premature ovarian failure. Wallerstein et al. [18] tested the karyotype of women with short stature and TS signs, and also found that 5% of the patients had a chimeric karyotype. Therefore, it is necessary to improve cytogenetics, oral mucosal smear or FISH detection for patients with short or TS signs. At the same time, when the karyotype of patients with chimerism is detected in peripheral blood, the chimerism ratio of cell lines cannot predict clinical phenotype and prognosis.

Sex chromosome abnormalities are the most common chromosomal abnormalities in infant chromosome identification. The incidence of sex chromosome abnormalities in newborns with sex chromosome abnormalities is about 1/400, while the birth rate of 47,XXX newborn girls with karyotype is about 1/1000. And the physiological defects of sex chromosome abnormalities are slighter than autosomal diseases, and XXX syndrome is lack of general abnormal characteristics, which brings some difficulties to genetic counseling and the correct choice of patients' parents. At present, after amniocentesis is diagnosed with 47, XXX syndrome, the fetal survival rate is high, and 99% of the fetuses can survive until birth. The families of children with super-female syndrome can not take measures to prevent the occurrence of chromosome non-separation. Studies have shown that the prognosis of patients with 47,XXX syndrome diagnosed before birth is better than that of patients diagnosed after birth, they can be better educated and can establish a better relationship with the outside world [19]. At present, there is no special treatment for super-female syndrome at home and abroad, clinicians should ask the child's medical history, combined with physical examination. Comprehensive evaluation of children's development, language, intelligence, behavior and emotion as soon as possible, the clinical manifestations of patients with super-female syndrome vary greatly, and the corresponding prognosis varies, some patients do not need treatment and can live a normal life. However, some patients are accompanied by severe congenital malformations or cognitive and psychological disorders, and their quality of life will be seriously affected. When stunting occurs, the behavioral development center of children is evaluated. Early developmental stimulation and speech therapy may be helpful for speech retardation. When learning, social or emotional disorders are found in school or pre-school age, you should consult a psychologist [20]. If adult patients have problems such as amenorrhea and menstrual disorders, they should go to the department of gynaecology to check for abnormal ovarian function in order to help better determine the timing and mode of childbearing, and estrogen therapy may be needed in patients with ovarian insufficiency [15]. Karyotype is an important factor affecting prognosis. To sum up, in clinical treatment for tall or short patients without special appearance, chromosome karyotype analysis should be improved to rule out chromosome diseases. Similarly, for patients with 47 Magi XXX karyotypes without special facial growth retardation, cytological tests, oral mucosal smear X-chromatin tests or FISH tests are needed to rule out the possibility of Turner syndrome [19].

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