

One man in every 500 is affected by Klinefelter syndrome. **Maybe you too?**

# Klinefelter Syndrome. Questions and Answers.



# Discover and Learn Something New.

## Questions and Answers.

### The Mission

To increase our knowledge about 47xxy Klinefelter syndrome in everyday life and to keep it fully up to date.

### The Booklet

This information booklet was written by members of our association for people affected by Klinefelter syndrome, relatives and interested parties. We would like to encourage you all to take an active interest in this topic. This booklet is intended to help you cope with everyday life as a person affected and to learn how to assess the quality of advice you receive. Because only if you know how the Klinefelter syndrome affects your own life, that of your child or your partner, then you can (co-) decide how best to deal with it and what is “right” and important for you.

Our information is based on current medical findings and the experiences of persons affected. In any case it is worth taking a look.

### The Association

The 47xxy klinefelter syndrome association (47xxy klinefelter syndrom e. v.) is a self-help organisation consisting of affected persons, relatives, interested parties as well as an advisory board. We pool our experiences, contacts and the knowledge of our network. And we do this gladly, well and voluntarily.

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## Klinefelter Syndrome, Cause and Diagnosis

### What is Klinefelter syndrome?

Klinefelter syndrome is a numerical chromosome aberration (deviation of the number of chromosomes) and is characterized by an extra X chromosome in men. The main symptoms of Klinefelter syndrome result from the disorder of testicular development, which causes both a decrease in sperm count and the production of the male sex hormone testosterone. Men with Klinefelter syndrome are virtually always infertile. Klinefelter syndrome is not uncommon, about one in every 500-1,000 men are affected. It is therefore the most common genetic disease in the male sex. In Germany between 41,000 and 82,000 boys or men are equipped with an additional X chromosome.

### Where does the name “Klinefelter syndrome” come from?

Klinefelter syndrome was named after the American physician Dr. Harry F. Klinefelter who, together with two colleagues, reported for the first time in 1942 on male patients with breast development, a severely reduced sperm count and increased excretion of the pituitary hormone follicle-stimulating hormone (FSH) in the urine. However, it was only 17 years later, in 1959, that the supernumerary X chromosome was first described as the cause of this syndrome by the British geneticist Patricia A. Jacobs.

### Which deviation of the chromosomes is behind the Klinefelter syndrome?

The human genetic make-up is not scattered in the cell nuclei, but is arranged on the chromosomes. Each nucleus usually has 46 of these. 44 chromosomes form 22 chromosome pairs (body chromosomes or autosomes) and 2 chromosomes are sex chromosomes (gonosomes). Men usually have one X and one Y chromosome, the chromosome set 46,XY, while women have two X chromosomes: 46,XX. One sex chromosome is inherited from each parent to the child. Klinefelter syndrome occurs when boys have an additional X chromosome in their body cells. The cells thus have 47 (47-XXY) instead of the 46 chromosomes usually found. The maldistribution

of the chromosomes may have occurred during maternal egg formation, paternal sperm cell formation or shortly after fertilisation.

### How does chromosomal maldistribution occur?

Chromosomal maldistribution is a random event, in a sense a whim of nature, which could not have been prevented by a special diet or by taking any medication. The surplus X chromosome can be inherited from the father or mother if a maldistribution occurs in the cell division processes during the formation of the respective sperm or ovum to be fertilised.

### What are the different types of Klinefelter syndrome?

Klinefelter syndrome is characterized by an additional X chromosome (47-XXY). Classic Klinefelter syndrome means that an additional X chromosome is present in all cells of the body. Classic Klinefelter syndrome is present in 90% of those affected. 7% of those affected have mosaic findings. In these cases an additional X chromosome is only present in one part of the body cells, while a normal set of chromosomes is present in the other part of the cells (46-XY/47-XXY). 3% of those affected have further additional X chromosomes (48-XXXY, 48-XXYY; 49-XXXXY). In the following we mainly refer to the actual Klinefelter syndrome with the continuous set of chromosomes 47,XXY.

### How can Klinefelter syndrome be diagnosed?

Physical characteristics of Klinefelter syndrome are an above-average height up to high growth, a reduced testicular volume, low body hair and occasionally an enlargement of the mammary gland. As a rule infertility is present; Klinefelter syndrome is frequently diagnosed in the medical examination of childlessness. During puberty and in adulthood, low testosterone levels with simultaneously elevated levels of the pituitary hormones FSH and LH in the blood can indicate the presence of Klinefelter syndrome. However, Klinefelter syndrome can only be reliably diagnosed by chromosome analysis. This examination is usually carried out in a human genetics laboratory. A small blood sample is sufficient for the examination. In order

to determine whether it is a mosaic form, an oral mucosa smear can also be taken. In the cytogenetic laboratory, several karyograms (sets of chromosomes) are taken from the blood/mouth mucosa cells. If an additional X chromosome is present in the examined cells, a Klinefelter syndrome is diagnosed.

### When is the diagnosis made?

Klinefelter syndrome is currently diagnosed in only 20-30% of those affected. Conversely, this means that 70-80% of those affected have no idea of their additional X chromosome for their entire lives! Of the 20-30% of those affected, approx. 70% are diagnosed in adulthood, 20% in adolescence and only approx. 7-10% in childhood.

### Can Klinefelter syndrome be diagnosed even before birth?

Klinefelter syndrome can be diagnosed by chance during a prenatal amniotic fluid puncture (15-18 weeks of pregnancy) or a chorionic villus biopsy (8-12 weeks of pregnancy). Klinefelter syndrome cannot prenatally be diagnosed by an ultrasound examination.

If Klinefelter syndrome is diagnosed prenatally as a chance finding, this can mean considerable uncertainty for the parents concerned, as they cannot assess the extent of the diagnosis at all. Thus they should be advised promptly and competently (e.g. specialist in human genetics, human genetic institutes at university hospitals).

### Is the prenatal diagnosis “Klinefelter” a reason to have an abortion?

Since most men with Klinefelter syndrome lead a largely normal life, an abortion is ethically problematic and not justified from the point of view of affected persons and parents. We would like to point out once again that approx. 70% of men affected in Germany have no idea at all about their additional X chromosome. Many of those affected lead a completely normal, independent life and work in many different professions.

## Symptoms and Concomitant Diseases

### What are the symptoms of Klinefelter syndrome?

In boys and men with Klinefelter syndrome, the testicles are underdeveloped, i.e. they remain below average. The testicular volume in affected persons is usually in the order of 1-3 ml (approx. the size of a small glass marble). Since most testosterone is produced in the testicles, men with Klinefelter syndrome have a testosterone deficiency. Testosterone is the most important male sex hormone, which plays a diverse role. It is important in sperm formation, regulates libido (sexual appetite or sex drive), but is also important in completely different areas such as fat metabolism, vascular function, psyche, formation of red blood cells, bone metabolism and hair growth (especially beard, breast and genital hair). A testosterone deficiency can therefore cause symptoms in different organs/tissues. However, these symptoms can vary greatly in persons with Klinefelter syndrome. An important consequence of testicular underdevelopment and testosterone deficiency is an early reduction or lack of sperm production. As a result, there are either too few sperm (oligospermia) in the ejaculate or, as in most men with Klinefelter syndrome, no sperm (azoospermia). For this reason, the vast majority of men with Klinefelter syndrome are infertile.

### Testosterone deficiency symptoms can be:

- » Above-average body height up to high stature
- » Reduced spermatogenesis (sperm formation), consequence: infertility
- » Sexual disorders (loss of libido, sexual potency disorders)
- » Sparse beard growth
- » Reduced muscle mass and strength
- » Changed fat distribution pattern (fat build-up especially in the hip area), growth of the mammary glands
- » Psychological symptoms such as fatigue, sleep problems, listlessness, increased sensitivity to stress, reduced attention, reduced self-confidence, reduced mood and even depression.
- » Sweat breakouts

- » Anemia
- » Bone loss (osteoporosis)
- » Enlargement of the prostate gland
- » Hair loss

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### Is Klinefelter syndrome associated with any concomitant diseases or side effects?

Yes. Compared to the general population men with Klinefelter syndrome have an increased risk of type II diabetes mellitus (old-age diabetes), osteoporosis (reduced bone density), gynecomastia (enlargement of the mammary glands), depression, epilepsy and the occurrence of thromboses. The risk of breast cancer in men with Klinefelter syndrome is increased by a factor of 50 compared to men with 46, XY, but is far below the normal risk for women. Since many men with Klinefelter syndrome remain undiagnosed for their entire life, the medical consequences of testosterone deficiency are usually not severe. This also shows that serious health problems caused by Klinefelter syndrome are the exception rather than the rule.

### What are the psychological aspects of Klinefelter syndrome?

In Klinefelter syndrome, the main focus of medical care is usually on tangible clinical aspects such as testosterone deficiency, bone health or fertility. However, there is also evidence that Klinefelter syndrome can affect temperament, personality and mental health.

In theory, a distinction must be made between the effects of testosterone deficiency on the brain and the psychological implications of the diagnosis or their consequences. In practice, however, this cannot always be easily separated. Both a perceived stigmatisation by fellow human beings and the importance of the desire to start a family and have children in the future turned out to be special risk factors, of which the latter can only be realised in men with Klinefelter syndrome, if at all, with considerable

medical effort. The reduced testosterone deficiency itself can also have an influence on the psyche.

In childhood and adolescence, disturbed attention and sometimes even increased impulsivity (ADHD) manifest themselves disproportionately. Language development disorders occur just as frequently as problems with reading and/or writing (reading and spelling disorders). There are indications that sometimes existing deficits in speech processing are accompanied by a better visual processing ability, which is apparently also caused by an unequal development of the corresponding brain areas. This in turn is reflected in an increased targeted attention and a special interest in details. In childhood, boys with Klinefelter syndrome sometimes stand out due to a behaviour that is associated with autistic behaviour. However, these are not as pronounced as in an autism spectrum disorder. It is primarily behaviour characterized by withdrawal, less interest in interacting with peers, and a particular passion for detail.

Sometimes boys and men with Klinefelter syndrome find it difficult to pursue their goals purposefully, their motivation is low. This can be noticeable in the pursuit of goals at school, during training or studies, and at work. Depression occurs frequently in adolescence and adulthood. More serious mental illnesses (e. g. psychoses) may occur somewhat more frequently in people with Klinefelter syndrome than in the general population.

Another factor that can influence satisfaction and mood is social interaction with others. Here it seems that men with Klinefelter syndrome sometimes have problems to correctly capture and interpret emotions in themselves and in their counterparts. In particular, the perception of unpleasant or annoying facial expressions or tones of voice of other people may be misinterpreted.

This, in turn, can sometimes lead to problems in social interaction, since the lack of recognition and thus also the lack of response to the mood of fellow human beings can lead to misunderstandings and irritations.

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**Treatment****Is it possible to correct the chromosomal anomaly?**

No. There are no possibilities to change the existing XXY chromosome set.

**How can the symptoms of Klinefelter syndrome be counteracted with hormone therapy?**

The testosterone deficiency is treated by a so-called testosterone substitution therapy. One option is the use of a testosterone gel, which is applied daily to the abdominal skin in the morning or evening. Many patients are very satisfied with this possibility of application, since they reliably achieve testosterone levels within the normal range. Another possibility is testosterone patches. However, many patients report skin irritations when using such patches.

A further therapy option are depot injections with testosterone enanthate by means of a syringe, for example into the thigh. 4 injections per year are sufficient to maintain a normal testosterone level. The disadvantage of these injections is the high peak concentrations of testosterone and the unpleasant fluctuations of level reported by many patients.

Testosterone substitution therapy should be started at puberty. The time and dose should be agreed between the adolescent, the parents and the doctor. If a Klinefelter syndrome is diagnosed after puberty, a specialist in endocrinology should be consulted so that testosterone substitution can be initiated promptly. Some affected persons show a more pronounced response to testosterone substitution than others.

Furthermore, men with Klinefelter syndrome often have a vitamin D deficiency. Therefore, vitamin D levels in adolescents and adults should be checked regularly. Especially in the “dark” winter months, vitamin D substitution (i. e. taking vitamin D tablets) should be carried out in consultation with the treating physicians. Vitamin D substitution is important for bone metabolism.

**What can happen if no testosterone treatment is started or the treatment discontinued without medical consultation?**

Testosterone therapy, the start of which is determined and ordered by the doctor (e.g. endocrinologist), should be carried out regularly according to the doctor’s instructions. Timely and continuous treatment is important for the well-being of the boy/man with Klinefelter syndrome. If a young person is not yet able to take care of the therapy by himself, you as parents are responsible for a smooth treatment.

If testosterone is not administered as prescribed by the doctor, this can lead to severe health consequences, especially during the growth phase. Without testosterone treatment, sexual desire (libido) is generally reduced compared to men with 46, XY. Since testosterone also affects the brain, a deficiency of this hormone can also promote the development of depression and other mental problems. Furthermore, a boy/man with Klinefelter syndrome needs the hormone for other metabolic processes, such as bone metabolism.

**What are important examinations before and during testosterone therapy?**

Before a testosterone treatment is started, an appointment should be made with an endocrinologist (hormone doctor). The hormone levels are measured by taking a blood sample. They serve as comparative values in the context of the subsequent testosterone treatment.

After the start of testosterone treatment, the doctor will monitor the course of therapy at regular intervals in order to assess the course of symptoms and determine possible side effects. As with all drugs, testosterone substitution can have side effects that do not necessarily occur in everyone. For example, changes in the blood count or an enlargement of the prostate can occur. The doctor will thus ask first whether the preparation is well tolerated and whether the symptoms have improved. In addition to monitoring the prostate, regular blood tests (including testosterone levels,



blood count, blood fat and blood sugar levels, vitamin D levels) should be carried out. Testosterone therapy lasts a lifetime and the dose can be adjusted occasionally by the attending physician.

### What is a bone density measurement?

Bone density measurement (also called osteodensitometry) is an examination in which the bone density of a person can be determined. A testosterone deficiency can lead to reduced or greatly reduced bone density (osteopenia/osteoporosis). People who are found to have reduced bone density may have an increased risk of bone fracture. Regular exercise, normal vitamin D blood levels, sufficient calcium intake and continuous testosterone treatment are important factors in increasing bone density.

A bone density measurement should be performed at the time of diagnosis and occasionally during the course of the procedure. A bone density measurement can be carried out either in the hospital, or also at an orthopaedist's or a radiologist's practice. The whole procedure is painless and takes about ten minutes; radiation exposure is negligible.

### Are there any other measures?

Furthermore, sports activities can not only help to improve bone density and stability, they also have a positive effect on physical and mental well-being, as with all other people.

Psychological counselling can be useful for those affected or families in order to prevent or reduce emotional difficulties. If an enlargement of the mammary glands develops (gynecomastia), it can be surgically removed. If the reduced testicle size leads to a lower self-esteem or self-confidence, the implantation of testicular implants can be considered. These testicular implants are made of highly polymerized silicone. They contain no gel and are easy to implant. The costs are usually covered by health insurance.

### What should be considered when administering psychotropic drugs such as atomoxetine methylphenidate (ADD/ADHD drugs)?

With Klinefelter syndrome an attention deficit disorder with or without hyperactivity is frequently diagnosed. In such a case, psychotropic drugs (often known as stimulants or ADD/ADHD drugs) can be helpful in addition to behavioural approaches. It is recommended to contact a specialist in paediatric psychiatry and psychotherapy in order to carry out the appropriate diagnosis and to plan and implement the corresponding therapy. Check-ups are a necessary part of a medicamentous treatment of an attention disorder.

#### Development and School

### Are there any physical characteristics that suggest Klinefelter syndrome at birth?

Boys with Klinefelter syndrome are usually quite normally developed at birth and do not differ from other children. Occasionally, however, testicular hypertension or hypospadias (abnormal location of the opening of the urethra) can be an indication of Klinefelter syndrome. However, children who do not have Klinefelter syndrome also suffer from testicular hypertension and hypospadias.

### Do all children with Klinefelter syndrome develop the same way

No general statement can be made about the development of boys with Klinefelter syndrome. While some boys have an unremarkable development (a large proportion of those affected are undetected), a small proportion have difficulties at school (e. g. concentration problems, learning problems, reading and spelling difficulties, increased impulsivity). At present it is not known why this subgroup shows such problems. In this regard for example, the paternal or maternal origin of the supernumerary X chromosome is the focus of discussion.



## How does a child with Klinefelter syndrome develop?

In childhood, the signs of Klinefelter syndrome are not very pronounced. From the age of four or five, an increased longitudinal growth can develop, which particularly affects the legs and is not the result of a testosterone deficiency. These boys can be calmer and more passive than other toddlers. The phase of defiance may be less pronounced than that of their siblings. Growth in childhood is slightly faster than among their peers, and their adult size is on average slightly above the average for the normal population.

## What cognitive disorders can occur?

If the diagnosis is made very early, language development delays or later difficulties in school can be observed in a large proportion of affected boys. It is not uncommon to find a reading and writing disability or difficulties in concentrating and a lack of drive. Here it is important that the children are supported therapeutically, for example by speech therapy, ergotherapy or tutoring. In serious cases one should also talk to the teachers to request special help to compensate for any disadvantages at school.

## Are children diagnosed with Klinefelter syndrome mentally retarded?

In Germany, the incidence of mental retardation in children and adolescents is estimated at about 1.8%. In comparison, those affected by Klinefelter syndrome only have a slightly increased risk of about 4%. According to current knowledge, the general intelligence of the vast majority of boys and men with Klinefelter syndrome is, if at all, only slightly below the intelligence level of their siblings. However, a partial performance weakness in the linguistic area (verbal IQ) is relatively frequent. The probability of disability is greater in those affected by the rarer forms (48-XXXY, 48-XXYY; 49-XXXXY) and increases with each additional X chromosome.

## What motor disorders can occur?

Some boys also show a somewhat delayed motor development: Sitting, crawling and running are learnt somewhat late; some boys with Klinefelter syndrome may show a certain clumsiness.

## Shall I tell my son's teachers about Klinefelter syndrome?

In principle, parents must decide for themselves whether they want to inform kindergarten or school teachers about the syndrome; it should be noted that most teachers do not know about Klinefelter syndrome and can therefore do little with the information alone. In order not to expose the child to unnecessary stigmatisation, we advise against informing teachers from the outset. However, if serious learning problems arise that make it difficult for your child to follow lessons, you may want to talk to the teacher about them in confidence in order to request extra help to compensate for any disadvantage.

## What does Klinefelter mean at puberty?

If left untreated, puberty can be delayed and more difficult in boys with Klinefelter syndrome than in other boys of the same age. A pronounced shyness, lack of confidence, a low libido and a reduced perception of one's own masculinity can lead to psychological problems and isolation. While in many affected boys testosterone production already dwindles during puberty (which is then incomplete), a real testosterone deficiency does not occur in most affected men until the third decade of life. Indications for a testosterone deficiency already during puberty can be, for example, a missing voice break. While the penis in men with Klinefelter syndrome can be of normal size, the testicles are usually as large as a small glass marble. Due to the testosterone deficiency, the growth plates of the bones do not close in time, so that affected men with testosterone deficiency often have an above-average body height with comparatively long legs. The lack of -/ low beard growth can be noticeable; also pubic hair and hairiness of the armpits is below average.

Since a testosterone deficiency leads to an increase in estradiol, an enlargement of the mammary glands (gynecomastia) develops in approx. 38% of all those affected. The muscles are usually so strong and more fatty tissue is deposited in the hip area.

## What are growth plates and what do they have to do with testosterone?

Humans are not born with fully developed bones. Rather, in the course of embryonic development, a cartilage rod develops into a structure that contains a bone nucleus in its middle. From this so-called primary bone nucleus, bone substance slowly develops through layer-by-layer reduction of cartilage and simultaneous formation of bone. Later, blood vessels advance into the end region (epiphysis) of the bone. This leads to the formation of a second (secondary) bone nucleus in the epiphysis area. The secondary bone nuclei often only fill the epiphysis space at the time of birth.

At birth, the width and length growth of the bones is not yet complete. Between the epiphyses, which are covered by joint cartilage, and the bone shaft there is a cartilaginous space, the epiphyseal joint. Further growth in length of the bone starts from these joints at the ends of the bone. This is why they are also called growth joints. With increasing age, the diaphysis and epiphysis become longer and stronger. At about 20 years of age, the growth joint ossifies. Once the epiphysis joint has closed, longitudinal growth is complete.

The growth itself is controlled by a hormone, the growth hormone STH (Somatotrophic Hormone). This hormone is released until the end of puberty. Through the interaction of the growth hormone with the sex hormones testosterone and estrogen, a growth spurt occurs at the beginning of puberty. When the level of the growth hormone decreases this process is slowed down. Finally, the growth plates close into a fine line.

If the growth spurt does not stop, it could be because the adolescent produces too little testosterone. Doctors specialising in Klinefelter syndrome are able to estimate at an early stage how much the growth in length relates proportionally to the actual body size. Early testosterone administration during puberty contributes to the premature closure of the growth plates of the bones to ensure that longitudinal growth stops and the actual possible body size is not reached.

## Is there a connection to bad teeth – taurodontism?

Dental anomalies can be an indication for diagnosing a genetic disease. Abnormal tooth and jaw findings appear to be more common in boys with Klinefelter syndrome. If taurodontistic teeth appear in a boy, there is a high probability of Klinefelter syndrome. Dentists have a great deal of responsibility here. A dental assessment is all the more important as it reduces the large number of men with undiagnosed Klinefelter syndrome.

### Partnership, Sexuality and Desire to Have Children

## What influence does Klinefelter syndrome have on first sexual experiences?

Klinefelter syndrome leads to reduced testosterone levels in young men. On the one hand, this can lead to shyness towards the opposite sex, and on the other hand the libido (sexual desire) can be reduced. Overall, sexual performance (potency) is reduced and there is often erectile dysfunction (inability to get or maintain an erection). Therefore, young men tend to be impaired in their sexual development by Klinefelter syndrome. However, the Klinefelter syndrome diagnosis does not affect sexual orientation in any way. Testosterone treatment usually leads to an increase in libido and potency.

## Can men with Klinefelter syndrome have partnerships and get married?

Men with Klinefelter syndrome can have happy partnerships and, of course, marry. Partnerships or marriages are neither better nor worse than marriages of men without Klinefelter syndrome. However, an unfulfilled desire to have children can become a burden on the relationship. Since about 15% of couples in Germany are unintentionally childless, there are numerous couples in the same situation. There are a variety of services offering help, including psychological counselling centres and fertility centres.

## Is my son/am I infertile?

Since the vast majority of men (>90%) with the classic Klinefelter syndrome have azoospermia, i.e. the absence of sperm in their semen, they are infertile. According to scientific findings, boys with Klinefelter syndrome aged 12-14 may still have residual spermatogenesis, so that they possibly still have some sperm in their semen (oligospermia). In addition, men with a 46XY/47XXY mosaic form are more likely to continue to have some sperm cells in the ejaculate. Whether azoospermia is present is determined by a urologist by means of an examination (spermiogram).

## What is a spermiogram?

A spermiogram is performed to assess whether and how many sperm cells are present in the ejaculate (sperm). This examination is carried out in a urological practice. In a locked single room the person seeking advice has to make a sperm donation by masturbation, which is then examined in the laboratory for the presence of sperm cells. Oligospermia means a reduced number of and azoospermia the complete absence of sperm cells.

## Can men with Klinefelter syndrome nevertheless produce biological children?

The new methods of reproductive medicine, especially the so-called Intracytoplasmic Sperm Injection (ICSI) method with previous Testicular Sperm Extraction (TESE) have led to the fact that men with Klinefelter Syndrome have repeatedly been helped to produce offspring. The figures are still too low to allow a general assessment of their chances of success.

## What is Testicular Sperm Extraction (TESE)?

Although most of those affected have no sperm cells in their ejaculate, functional sperm cells may be present in the testicular tissue. TESE (abbreviation for testicular sperm extraction) or micro-TESE is a surgical procedure on the testicle that is usually performed under general anesthesia. During this operation, tiny tissue samples of the testicles are taken (testicular biopsies) and then examined under a microscope for the pres-

ence of sperm cells. If sperm cells are found, they are cryopreserved, i.e. frozen at minus 196°C, and can later be used for family planning by means of the Intracytoplasmic Sperm Injection (ICSI) method. ICSI is an artificial insemination method in which a thawed sperm cell is injected directly into a previously removed ovum of the partner in the laboratory. After this artificial insemination, the fertilised ovum is inserted into the partner's uterus. If this artificially fertilised egg cell implants into the uterus like a normally fertilised egg cell, pregnancy begins. At present, however, only every 4-5<sup>th</sup> ICSI attempt leads to a successful implantation.

## What has to be taken into consideration regarding TESE?

The possibility of a TESE should be discussed relatively early with the parents or the boy, since the success of such an operative measure is favoured by a young age and still existent testosterone production. A TESE should definitely be carried out before starting testosterone therapy, as testosterone treatment stops sperm production and thus reduces the chance of finding sperm cells. Since most children at this age are still too young to think about their own children, parents should look ahead to the future and act in the interest of the son who will grow into a man, even though of course the boy should be informed accordingly and agree. If a TESE is carried out early, your son has the best chance of having children of his own later on. When your son has grown up, he can decide for himself whether he wants to use the frozen sperm cells for ICSI or not. Thus the parents take an important decision in their son's childhood, which will have a decisive influence on the future adult life of their child. A TESE in adulthood is associated with significantly lower chances of success, but should be carried out anyway in consultation with the attending physicians if the person attended wishes to have children.

## Who covers the costs of a TESE/ICSI?

Usually, most of the costs for a TESE (or micro-TESE) are covered by public health insurance companies. Nevertheless, the patient's own contribution

is between 500 and 1,000 Euro. While most public health insurance companies cover about 50% of 3 ICSI treatment costs, there are some health insurance companies that offer 100% coverage.

## Will the biological sons of a man with Klinefelter syndrome also get Klinefelter syndrome?

Recent studies suggest that biological children of men with Klinefelter syndrome (sperm obtained by TESE) have no additional X chromosome and thus no Klinefelter syndrome (e.g. Greco et al. Hum Reprod. 2013). However, since research in this area is still in its infancy and the number of cases is relatively low, no generally valid data can be provided at present.

## Are there alternatives in the case of a desire to have children?

If functional sperm cells can neither be obtained from sperm nor through TESE, there is no other way of fathering biological children. However, there are alternative possibilities to fulfil a couple's wish to have children. For example, it is possible to fertilise the partner's female egg with donor sperm (another person's sperm). This method is also an artificial reproduction method which is carried out in a fertility centre.

Furthermore, there is the option of adoption or taking in foster children.

### Inspiration

## When and how do I tell my child?

Many parents don't really know how and when to tell their son that he has Klinefelter syndrome. In early childhood, at school, or at the beginning of puberty? In our experience, the earlier you talk about it with your son and the more naturally you deal with it, the easier it is to live with it in your family. Of course, you should talk to the boy in a way which suits his age; it is important to take his level of maturity into account. Perhaps the following letter written by an experienced physician, used in his practice to help boys (aged around 12–15 years) understand their special situation,

will be helpful to you. Our thanks go to Dr. Achim Wüsthof, who personally made this contribution available to Mr. Schorpp for publication.

### Dear Max,

Today I got the results of the lab tests on your blood. Now I can explain to you why your testicles and penis are slightly smaller than those of your friends. You have a special feature in the cells of your body that you share with about one man in 500. We have diagnosed you with the so-called Klinefelter syndrome. Klinefelter is the name of a North American doctor who observed men whose testicles did not grow sufficiently. Later, other researchers discovered that these people had an additional X chromosome.

What does this mean? Our body is made up of millions of cells, like a brick house. In every single cell of the body, from the white blood cell to the muscle fibre, there is a precise blueprint: the chromosomes. There the hereditary information lies in the so-called genes, which determine whether the eyes are to be blue or brown, whether the nose becomes pointed or hooked, whether someone becomes bald or not. Each cell has 46 such chromosomes, and there are two sex chromosomes called X and Y.

When a baby comes into being, half of all chromosomes comes from the mother and the other half from the father. Men have either X or Y chromosomes in their sperm cells; in the maternal egg cell there is always an X chromosome. When a father's X chromosome meets a mother's X chromosome, a girl is formed; when X and Y come together, it becomes a boy. In exceptional cases, however, three sex chromosomes meet and a chromosome set of 47.XXY is formed: a boy with Klinefelter syndrome. A man with an additional X chromosome is by no means more "female" than one with a chromosome set of 46.XY; neither does this chromosome feature make him ill and he could well live with it to become 100 years old. Some boys with Klinefelter syndrome learn to speak a little later and school is not that easy for them. But with many of them you don't notice a thing, except that they are often very tall.

What practically all young men with Klinefelter syndrome have a problem with, however, is the development of the testicles. Usually the testicles start to grow at the age of 11, 12 or 13: the beginning of puberty. They produce the male sex hormone testosterone, which changes the body: Hair sprouts in the genital area, under the armpits and in the face, the penis grows and the voice becomes deeper. Sperm cells are formed in the testicles for reproduction. Many boys with Klinefelter syndrome initially produce enough testosterone so that their physical changes hardly differ from those of their peers. However, their testicles remain small and sometimes the penis develops too slowly. Some have swelling of the mammary glands. And that's why you, dear Max, came to me.

We have now found in you the Klinefelter chromosome set of 47.XXY and also that your testosterone level is somewhat low. Therefore I wanted to recommend that you start with a testosterone treatment. This gets into your body either in the form of injections, a gel to be applied to the skin, plasters or capsules. This allows us to normalize your puberty development.

What we can't treat, unfortunately, is the disorder in the testicles. Your testicles are probably not able to produce sperm cells. I can well imagine that it is not a nice idea for you to not be able to have children of your own later on. But maybe medical research will be a step further by then and it will be possible after all. In a few adolescents, sperm cells can already be obtained today, which are then stored in special deep freezers until the desire to have children arises.

The testosterone treatment would damage these sperm cells. The examination to see whether such cells are formed at all should thus be carried out before hormone therapy. With the help of testosterone your puberty will be completely normal in any case. Your penis will grow, you can have a girlfriend and have sex with her, meaning that you will not differ from any other young man except for having small testicles. This is the aim of our treatment and it is guaranteed to work. I can promise you that. If you have

any questions, we will discuss them in detail at our next appointment in the practice. In the meantime I wish you all the best.

Your Dr. Achim Wüsthof, Endokrinologikum Hamburg

## How do I find the right doctor?

The first suspicion of Klinefelter syndrome in children is usually made by the paediatrician. A human geneticist (doctor for genetic diseases) then diagnoses Klinefelter syndrome through chromosome analysis. In order to ensure successful therapy, treatment by specialists is advisable. Treatment is interdisciplinary (different medical fields are involved). Endocrinologists (hormone specialists) check the testosterone levels at regular intervals and are the best contact persons for testosterone substitution therapy. Urologists (urinary and male genital organs specialists) carry out examinations of the prostate, testicles and TESE. In both these medical fields there are specialists for children and adolescents. Furthermore, in some cases psychotherapist care is a good complement to medical treatment in order to deal with the diagnosis emotionally. If there are more severe attention or learning problems or psychological disorders in childhood and adolescence, it is advisable to contact a doctor for child and adolescent psychiatry and psychotherapy.

### Endocrinologists for children and adolescents:

<https://memlist.dgked.de/>

### Endocrinologists for adults:

<https://www.endokrinologie.net/arztsuche.php>

### Speech therapists:

<https://www.dbl-ev.de/service/logopaedensuche.html>

### Child and adolescent psychiatry, psychosomatics and psychotherapy:

<http://www.dgkjp.de/kliniken>

### Human geneticists:

<https://www.gfhev.de/de/beratungsstellen/beratungsstellen.php>

### Fertility centres:

<https://www.deutsches-ivf-register.de/mitgliedszentren.php>

## Glossary

### Technical terms used in urology, andrology, endocrinology, genetics and reproductive medicine



#### Amniocentesis

Amniocentesis is an amniotic puncture. An amniotic puncture is a form of invasive prenatal diagnosis that makes it possible to detect or rule out a genetic disease in the developing fetus (unborn child). Trisomies and monosomies can also be detected by amniocentesis. A needle is used to remove some amniotic fluid from which the genetic material of the unborn child can be isolated and then examined.

#### Anamnesis

The patient's medical history. This includes all previous illnesses and operations. Alcohol and cigarette consumption are also inquired.

#### Androgens

The male sex hormones are called "androgens". There are many different androgens, of which testosterone is the most important. Androgens play an important role in the development of male sexual characteristics. They are also responsible for the development of secondary sexual characteristics such as beard growth, body hair and voice break. Androgens are formed in the adrenal cortex and testicles.

#### Andrology

Andrology is a special field of medicine that deals with the reproductive function of men and its disorders. Andrology is thus concerned with the treatment and research of all male-specific ailments (e.g. erectile dysfunction, diseases of the penis). Andrology is the male correlate of gynaecology.

#### Aneuploidy

Aneuploidy is a numerical chromosome aberration in which additional

chromosomes are present or are absent from the usual set of chromosomes. Klinefelter syndrome is caused by an aneuploidy of the sex chromosomes.

#### Autosomes

Term for all chromosomes of a chromosome set with the exception of sex chromosomes. A normal chromosome set has 44 autosomes plus 2 sex chromosomes. The sex chromosomes in women are usually XX and in men XY.

#### Azoospermia

Azoospermia describes the absence of sperm cells in the ejaculate (sperm).



#### Barr body

Women usually have two X chromosomes, one of which is inactivated. This inactivated X chromosome is detectable in the cells as a Barr body. X inactivation occurs early in the embryonic stage. A large part of the genes on this "switched off X" are therefore not used. This is normal. In men with Klinefelter syndrome, one of the two X chromosomes is also "switched off" in each cell.

#### Benign Prostatic Hyperplasia (BPH)

Benign enlargement of the prostate gland

#### Biopsy

Tissue sampling



#### Cryopreservation

Cryopreservation is the storage of cells or tissue by freezing them in liquid nitrogen. This method makes it possible, for example, to store sperms for several years in order to thaw them if necessary for artificial insemination, e.g. ICSI treatment.

## D

**Cryptorchidism (testicular hypertension)**

Cryptorchidism means that one of the two testicles is not in the scrotum at the time of birth. This is the most common anomaly of the urogenital tract.

**Digital rectal examination (DRU)**

The DRU is a finger examination of the rectum and the adjacent organs, especially the prostate. It provides initial clues for diseases of the prostate and rectum. The examination is simple, quick and painless.

**Diploid**

A set of chromosomes is “diploid” if it is present in duplicate. In most multicellular organisms (and also in humans), most cells of the body have a diploid set of chromosomes. A set of chromosomes is “haploid” if it is a simple set. In humans, only the gametes = (cells for sexual reproduction, i. e. egg and sperm cells) are haploid.

## E

**Embryo**

After an egg is fertilised by a sperm cell, it divides and from then on is called an “embryo”. This name is retained until the end of the third month of pregnancy. Then we speak of a fetus or foetus.

**Endocrinologist / Endocrinology**

Endocrinology is the science of endocrine glands. This includes, for example, the thyroid gland, the pancreas or the adrenal glands.

## F

**Fertilization**

The fusion of sperm cell and egg cell. The result is a zygote.

**FISH**

Fluorescence in situ hybridization is a cytogenetic method to visualize specific chromosome segments with fluorescent dyes. This method is carried out by geneticists. This analysis allows the detection of structural alterations of the chromosome set.

## G

**Follicles**

Fluid-filled follicles in which the egg cells are located. The follicles mature in the ovaries.

**Follicle puncture**

Ultrasound-monitored egg extraction by means of a hollow needle through the vaginal wall. As a rule, a short-acting anaesthetic is required.

**Free Testosterone**

More than 97% of testosterone in the blood is bound to proteins (e.g. sex hormone binding globulin and albumin) and only about 1-3% is present as a free hormone. The sum of the free testosterone and the weakly albumin-bound testosterone is the bioavailable testosterone (approx. 35% of the total testosterone).

**FSH**

The follicle stimulating hormone (FSH) is a sex hormone produced in both men and women in the anterior pituitary (frontal lobe of the pituitary gland). In women, FSH causes the ovaries to mature from follicles to mature eggs and ovulation. In men, FSH stimulates sperm formation (spermatogenesis).

**Gonads**

A gonad is the sex organ in which some sex hormones and germ cells are produced. The gonads of the male sex are called testicles, those of the female sex are called ovaries.

**Gynecomastia**

Gynecomastia is the enlargement of the male mammary glands on one or both sides. Excess mammary gland tissue can be removed by a surgical procedure called “mastectomy”.





### Habit

Appearance, Constitution

### Hematocrit

Hematocrit refers to the proportion of cellular components in the volume of blood. It describes the fluidity of the blood and is expressed as a percentage. The norm value is about 46% for men and about 41% for women. If the hematocrit rises, the blood becomes more viscous and flows more slowly. This increases the risk of developing thromboses (blood clots). Red blood cells account for more than 95% of hematocrit. White blood cells and platelets account for only a small proportion of hematocrit.

### Haemoglobin

Haemoglobin is an iron-containing protein complex found in red blood cells (erythrocytes) and is important for oxygen transport. It also gives the blood its red colour.

### Human Genetics

Human genetics is the medical discipline that deals with congenital or hereditary diseases. The tasks of a human genetic institute include, for example, human genetic counselling and pre- and postnatal genetic analysis of various hereditary diseases.

### Hypogonadism

Hypogonadism generally refers to the subfunction of gonads, e.g. the testicles. Depending on where the disorder occurs, a distinction is made between primary hypogonadism (disorder in the testicle or ovary), secondary hypogonadism (disorder at the level of the pituitary gland) and tertiary hypogonadism (disorder at the level of the hypothalamus).



### ICSI

IntraCytoplasmic sperm injection, ICSI for short, is a method of artificial insemination. The sperm cell of the man is transferred directly into the cytoplasm (ooplasm) of an egg cell.

### Idiopathic

Without any apparent cause. E.g. idiopathic hypogonadism: Hypogonadism is present, but despite medical examinations the underlying cause could not be found.

### Impotence

The word impotence is the generic term for the three dysfunctions:

1. Erectile dysfunction (inability to get an erection or maintain it for long enough)
2. Anejaculation (inability to get ejaculation)
3. Impotentia generandi (inability to produce children despite undisturbed erectile function)

### Infertility

### Insemination

Insemination is the transfer of the male semen into the female genital tract. It is a common form of artificial fertilisation.

### IVF

In vitro fertilisation (Latin for “fertilisation in glass”), the fertilisation of the egg and sperm cell does not take place in the woman’s body, but “artificially” in the laboratory. It is a common method for artificial insemination.



### Karyogram

A karyogram is the ordered representation of all chromosomes of a cell. The chromosomes are ordered according to morphological properties such as size, centromere position and banding pattern. Karyograms are created to determine the karyotype, i.e. the chromosome composition of an individual.

**Klinefelter syndrome**

Klinefelter syndrome is a numerical chromosome aberration (deviation of the number of chromosomes) and is characterized by a surplus X chromosome in men. Klinefelter syndrome is not uncommon, about every man in 500-1,000 men is affected. It is thus the most common genetic anomaly in the male sex. In Germany alone, 41,000-82,000 boys or men have an additional X chromosome.

**LH (luteinizing hormone)**

The luteinizing hormone is produced in the pituitary gland and is one of the hormones that play an important role in reproduction. In women it promotes ovulation and the formation of the corpus luteum. In men it controls the formation of sperm, among other things.

**Meiosis**

Meiosis is the form of nuclear and cell division in which a diploid cell (cell with double set of chromosomes) becomes four daughter cells with a haploid (single) set of chromosomes. Meiosis thus halves the set of chromosomes. This is necessary for the gametes (sperm and oocytes). When the egg and sperm cells are fertilised, a complete set of chromosomes is formed again.

**Metabolic Syndrome**

Metabolic syndrome is not an independent disease, but a combination of various diseases and risk factors for cardiovascular diseases. The following symptoms usually appear together in metabolic syndrome: severe overweight (obesity), fat metabolism disorders, high blood pressure, elevated blood sugar level or diabetes mellitus type II. Factors which contribute to the development of a metabolic syndrome are above all a lack of exercise and a calorie-rich diet.

**Monosomy**

Monosomy is a form of gene mutation (aneuploidy) in which one chromosome is missing in the diploid (double) set of chromosomes. Turner syndrome, for example, is a monosomy. Instead of the usual female karyotype (46,XX), women with Turner syndrome have one X chromosome too few (45,X).

**Mosaic**

A cell mosaic means that a genetic aberration exists only in a part of the body cells. About 7% of men with Klinefelter have such a mosaic. This means that the additional X chromosome is only present in a part of the body cells, while the other part of the body cells has the usual male chromosome set 46,XY.

**Non-disjunction**

Non-separation. Error in meiosis in which two chromosomes or sister chromatids do not separate correctly. The result is a numerical chromosome aberration, e.g. aneuploidy (see aneuploidy). Non-disjunction is an absolute random event and occurs in both men and women.

**Obesity**

Obesity means severe or pathological overweightness. According to the WHO, obesity occurs when people have a body mass index (BMI) in excess of 30 kg/m<sup>2</sup>. To calculate the BMI, one divides one's own body weight by the body height squared (weight/size<sup>2</sup>). In addition to genetic factors, over-eating and lack of exercise play a major role in the development of obesity.

**Oedema**

Accumulation of water in the tissue. There are numerous causes, including severe protein deficiency or cardiac/kidney insufficiency.

**Osteopenia**

Osteopenia is a reduction in bone density, it is a precursor of osteoporosis.



### **Osteoporosis**

With increasing age, the density of the bones declines. This is normal. However, osteoporosis denotes an enhanced decrease in bone density, which can lead to an increased risk of fractures. Physical activity and movement strengthens the bones.

### **Phenotype**

The phenotype, also called appearance, describes in genetics the set of all characteristics of an organism. The phenotype is determined by the interaction of genes and environmental factors.

### **Pituitary gland**

The pituitary gland (hypophysis) is a pea-sized gland on the underside of the brain that is involved in controlling various bodily functions through the release of various hormones. The hormones released from the pituitary gland in turn stimulate downstream glands (e. g. thyroid gland or adrenal glands) to produce hormones independently.

### **Poly-X Syndrome**

Poly-X syndrome is a genetic mutation in humans. Here, the chromosome set of the cells consists of three (triple X syndrome) to eight X chromosomes instead of two X chromosomes. The frequency of such a modification is 1:1,000.

### **Prenatal diagnostic testings**

Prenatal diagnostic testing denotes various examinations on fetuses (unborn children) or pregnant women. A distinction is made between “non-invasive” examinations, in which examinations are carried out only outside the body, and “invasive” examinations, which are carried out inside the body. Non-invasive examinations include, for example, various ultrasound examinations and examinations of the hormone concentration in the maternal blood. Invasive diagnostics include chorionic villus biopsy, amniotic fluid analysis or umbilical cord puncture.



### **Prostate (prostate gland)**

Part of the man’s internal sex organs found in the pelvis below the bladder and surrounding the urethra.

### **Prostatitis**

Prostate inflammation

### **PSA (prostate-specific antigen)**

The prostate-specific antigen is an enzyme that is added to the ejaculate as a physiological secretion product of the prostatic ducts and serves to liquefy the seminal fluid. An elevated PSA level may indicate prostate cancer.



### **Reproductive Medicine**

Reproductive medicine deals with reproduction and its disorders. The main task of reproductive medicine is to help with unwanted childlessness.

### **Sterility**

Infertility

### **Sperm**

Male germ cell



### **TESE**

TESE (abbreviation for testicular sperm extraction) or micro-TESE is a surgical procedure on the testicle that is usually performed under general anesthesia. During this operation, tiny tissue samples of the testicles are taken (testicular biopsies) and then microscopically examined for the presence of sperm. If sperm can be found, they are cryopreserved, i.e. frozen at minus 196° C, and can later be used for family planning using the Intracytoplasmic Sperm Injection (ICSI) method.

### **Testicular biopsy**

Tissue removal from the testicle under anaesthesia

**Testicular prosthesis**

A testicular prosthesis is a plastic testicular implant.

**Testosterone**

Most important male sexual hormone

**Transurethral**

Through the urethra

**Transurethral prostate resection (TUR-P)**

Surgical technique in which prostate tissue is removed through the urethra.

**Triploidy**

Triploidy (triploid, “triple”) in genetics is understood to be a peculiarity in which a living being or a cell has three (Latin Tri = three) complete haploid chromosome sets ( $3n$ ). Triploidy is known in animals and plants. However, a triploidy can also be present in a fertilized human egg cell. Since a triploidy is not viable in humans, however, a triploidy is a frequent cause of an abortion (miscarriage).

**Translocation**

In genetics, translocation is a chromosome mutation in which chromosome segments are moved to another position within the chromosome population.

**Thrombosis**

Thrombosis occurs when a blood clot blocks a blood vessel, especially a vein. It is dangerous when a part of this blood clot enters the lungs via the heart and blocks the blood vessels necessary for breathing.

**Ullrich-Turner Syndrome (UTS)**

A UTS is present if one less X chromosome ( $45, X0$ ) is present in a woman instead of the usual  $46, XX$  chromosome set. This deviation (anomaly) is called monosomy X and is caused by a maldistribution of chromosomes



during cell division. The frequency of a Turner syndrome is given as approx.  $1:3,000$ - $1:5,000$ .

**Urologist**

Specialist in diseases of the urinary tract. A urologist therefore treats both men and women.

**Vitamin “D”**

Vitamin “D” is a fat-soluble vitamin and plays an important role in the regulation of the calcium level in the blood and is thus involved in bone metabolism. Vitamin D is produced within our body by the sun’s rays on the skin. Men with Klinefelter syndrome often have a vitamin D deficiency. For this reason, vitamin D levels in adolescents and adults should be checked regularly. Especially in the “dark” winter months Vitamin D substitution (i. e. taking vitamin D tablets) should be carried out in consultation with the treating physicians. Vitamin D substitution is important for bone metabolism.

**XX man**

An XX-man is a person who has a male appearance (phenotype) although he has a female karyotype ( $46, XX$ ). This means that both sex chromosomes are X chromosomes, while the Y chromosome normally necessary for the formation of the male phenotype is missing. The frequency of occurrence is  $1: 10,000$  to  $1: 20,000$ .

**XYY syndrome**

XYY syndrome is a numerical chromosomal aberration of sex chromosomes. Instead of the usual male chromosome set  $46, XY$ , men with XYY syndrome have an additional Y chromosome ( $47, XYY$ ). Most people are healthy and therefore the term “syndrome” is currently under criticism.

**Y chromosome**

The Y chromosome is a sex chromosome. It causes the formation of the male phenotype.





## Zygote

After the fusion of sperm and oocyte, a zygote develops.

## Testimonials

### The most important question in life is: How does a boy or man live with Klinefelter syndrome? The answers can be found in life.

#### Franz: My Life with Klinefelter Syndrome

I got married. When, after two years of marriage, there were still no children, my wife and I went to a dermatologist in Regensburg. This doctor was very unfriendly, rude as well as tactless. After some examinations and an analysis of the spermiogram I got the diagnosis, and it was like a punch in the gut! With no time to prepare my wife and I got the result flung in our faces:

“It is impossible that you can ever have children,” he said to me. “The testicles are as small as cherry stones, and a fertility cannot be achieved medically either”. With the remark: “I have no more time now”, he left. Klinefelter syndrome was not mentioned at all. It was a shock for both of us, especially for me. At that time I needed weeks to digest this experience. After about a year we tried again and went to see another dermatologist. After thorough examinations (spermiogram and testicular biopsy) and very empathetic conversations Klinefelter syndrome was diagnosed.

For further examination I was referred to the Department of Andrology at the University Skin Clinic in Erlangen. In the course of a long and careful conversation between me, my wife and the attending doctor a hormone treatment was mentioned for the first time. The treatment was started in 1972 (when I was 33 years old) with Testoviron Depot 100 mg for three months, at three-week intervals. After that a new check-up was carried

out in Erlangen and the medication was increased to 200 mg for a period of one year. At the end of the year a new examination was done after which I received the full dose of Testoviron Depot 250 mg every three weeks until 1980. Since the hormone level had dropped too much towards the end of the three weeks the interval was shortened to 14 days. Due to the onset of prostate enlargement, the intervals were later extended to 17-20 days.

Since it was not possible to have children naturally, we adopted three children, a son and two girls. We are a happy family and now have nine grandchildren.

In 1992 I applied for a disabled ID card which was granted to me with a 50% degree of disability. Due to further deterioration after two years I applied for and received a 70% degree of disability. The ID card was extended for life in 2010.

I would certainly have been spared many things if the hormone treatment had started at the beginning of puberty. Testosterone therapy, which I have been receiving for over 35 years, has improved many of my symptoms and my joy of life has increased continuously. Today I am 80 years old and I feel better than when I was young. Most certainly I would have been spared further physical and mental problems if the causes of my symptoms had been discovered earlier.

One can only hope that by educating people and most of all through medical progress, such mistakes will happen less often.

In 1992 the first German Klinefelter Syndrome Association was founded, of which I was a founding member. In 1993 I founded a self-help group for Klinefelter syndrome in Regensburg. It was the first self-help group for this syndrome in the whole of Germany. In spring 2007 I received the medal of the Order of Merit of the Federal Republic of Germany for this activity from the Federal President Horst Köhler.

In 2012 a new association for 47xxy Klinefelter Syndrome was launched. Through working with this new association I would like to pass on my many years of experience with KS to those affected who are seeking advice. Due to the tragic death of its chairman Mr. Johnki in September 2017 I was elected as his successor (1<sup>st</sup> chairman). I hope that I will be able to work in the new association for several more years.

## Disease and Early Death Due to Untreated Klinefelter Syndrome

I would like to tell you about my first husband, who I must assume was affected by Klinefelter syndrome. It quite certainly led to great suffering and to his untimely death at the age of 60. Unfortunately he rejected all signs of this syndrome and the possibility of therapy.

My husband was born the only child of a single mother and brought up mainly by his grandparents. Already at the age of 9 he was very overweight. He could not keep up in school sports. After an outstanding Abitur he studied medicine, but failed the second state examination. He then built up a career as a pharmaceutical sales representative and later as a management consultant, which was initially more successful but later less successful.

After we got married and the economic conditions were right, we wanted to start a family. But after I had not become pregnant for a long time, and some possible reasons were ruled out for me, he had a spermogram done. The andrologist attested his sterility and diagnosed a hypogonadism. He mentioned a medication, but my husband rejected this option. Over the years we had a total of three children with the help of heterologous (or today: donogenic) insemination and should have been a normal happy family. But it wasn't until the youngest child was six years old that I finally understood that not only was I unhappy in my marriage, but the children were missing something as well. There was simply no interpersonal relationship with their father. I decided to part with him, which must have been very

painful for him. The children remained with me. Although there were visits at first, we lost touch with him more and more. Over the years he had such problems with his last girlfriend that he forced his eldest son by threatening to commit suicide to help him overcome their psychiatric crises, which put a massive strain on our son and ultimately led to a break in contact. The relationship with the second son broke off because my husband, who had previously been conscientious in official matters, refused to cooperate and sign Bafög (state tuition allowance) applications. With our daughter he had long since lost touch.

We watched his social decline and his increasing diseases from afar. One factor that accelerated this was that he had no friends or acquaintances except for a single telephone contact. Looking back I realized that he had never socialised easily before. For him this was almost only possible in the context of a professional or other function.

Also in retrospect I realized that, without being particularly athletic, I had been the stronger of the two of us, which was evident, for example, in gardening or renovations. All in all, he tired much too quickly in all his activities. He was not yet 45 when his family doctor diagnosed diabetes mellitus type 2. However, he did not follow the dietary advice and took the medication irregularly. After our separation his general condition worsened rapidly and he lost a lot of weight and strength. A few years later he was given a by-pass. Then over the years he became so immobile that his heels were sore to the bone. Further hospital stays because of various inflammations followed. And after his death we learned which diseases had developed over his last few years: in addition to other complaints and high blood pressure, several diagnoses had been made that related to the heart alone. Each one of these conditions is already highly dangerous and restricts a person's lifestyle considerably. His diabetes, which was by that time subject to insulin, was completely derailed; the kidney was chronically impaired, and a frailty syndrome had developed. This means that he looked like a frail eighty-year-old.

At the emergency room he was sent to the intensive care unit straightaway. He suffered from an acute kidney failure, i.e. he was totally dehydrated, and on the other hand large amounts of fluid had formed oedema at certain points. Infections were not only present on the feet, in the meantime also in the urinary tract, in addition there was pneumonia, complete acidosis and anaemia caused by the infections. Even our intensive care medicine was no longer able to save him, and he died much too young. The processes that had taken place over the years are after all not reversible.

Another reason why I am so shocked about this development, which seems to me like it was an ordeal, is that I think it was not necessary. If he could have faced up to the diagnosis, he could have substituted testosterone, and he would have been stronger, more efficient, more active in his life. Because it had almost always been me who made suggestions, who initiated, who organised. The tendency towards depression, which had probably been present in the past, but certainly had increased in the last decade and a half, could have been avoided. With a body with masculine muscles and with a brighter mood, he could have more easily implemented the medical advice for a healthy diet and sufficient exercise. Diabetes would probably not have broken out to that extent, since it develops in untreated Klinefelter as a result of the lack of muscles.

It keeps bothering me that the syndrome is diagnosed so rarely even today and even then is often not treated. "One is still healthy" is then said. I hope I have shown how fatal it can be to take Klinefelter lightly.

### Desire to Have Children with Klinefelter Syndrome Accompanied by Asperger Autism

I was very surprised when one day I noticed that Asperger autism was mentioned in connection with Klinefelter. How could there be a connection? But in our case it turned out to be the case. Again, this has never been diagnosed. But the first time I happened to get my hands on literature about Asperger autism, I knew, "Yes, this is it!" This explained the misery I had in my marriage and what the children missed regarding interpersonal

contact. I was born in 1959, and my parents, as war children, were rather emotionally reserved, which I was not aware of. So I slid into marriage with my husband without really noticing what I was missing.

Today I read with concern the reports about young families which come about with the help of sperm banks or complex fertility medicine. It is not that I do not grant them their happiness. No, I only know what suffering it is for everyone involved if the relationship between the parents is not sustainable in the long run. What hours of crying, what feeling of being trapped because you feel guilty towards a partner who, in the case of a separation, would be burdened with alimony payments for children who are not his or her own, or who have only "artificially" come into being. The idea that the relationship between the children and him cannot last long, i.e. that sooner or later he will no longer keep in touch, but will still have to pay or fill out Bafög applications, disclose private and financial matters, etc. This is a horrible situation that I do not wish for anyone. And what about the kids? Going around the world with open eyes already at kindergarten age and seeing how much more affectionate other fathers are with their children? What a loss, what a lack right from the start!

I have read with admiration one or two reports about Asperger autists, and I think that there are certainly many of them today who develop differently than was the case with my husband, who reflect on their behaviour, who learn.

Nevertheless, I would advise any young woman who plans to have children with a man with Klinefelter syndrome to read some life reports or stories about Asperger. And if they seem familiar to her, she should consider carefully what to do.

Our gynaecologist, who helped us with the first child, told us that at that time psychological counselling was offered at the university clinic for parents who wanted children. My husband considered psychology completely superfluous and I was quite loyal to him, so we did not make use of it. If I



had read a testimonial somewhere that would have made me more aware. I would have insisted on the consultation and perhaps it would have turned out that I would have to part with my husband or with the desire to have children. Even though I love my children very much today and am reconciled with my history, I would have been spared a lot.

Finally, a vivid example concerning relationships: For many Asperger autists, a relative who dies is simply gone (e.g. in “Buntschatten und Fledermäuse: Mein Leben in einer anderen Welt” (“Colourful Shadows and Bats: My life in another World“ by Axel Brauns). Imagine your common child dies! So for your partner, the child is simply gone. How can you mourn at the side of someone like that? You will hardly be able to bear it!

## Testicular Sperm Extraction

At the age of 27 I was diagnosed with Klinefelter syndrome. An examination with a spermogram showed the presence of azoospermia (the absence of sperm cells in the sperm) and thus dispelled last hopes to have children in a natural way. So there was no doubt anymore. There is no possibility for me to conceive biological offspring naturally. I was angry, sad and desperate. Why me? The realization that I was infertile caused a diminished male self-perception in me. This fact had (and has) effects on my self-image and my self-confidence. Maybe a psychological consultation could help in this regard.

I was told of the possibility of a TESE. The TESE (abbreviation for Testicular Sperm Extraction) is a surgical procedure on the testicle, which is usually carried out under general anesthesia. During this operation, tiny tissue samples are taken from the testicles and then microscopically examined for the presence of sperm. If sperm are found, they are cryopreserved, i.e. frozen at minus 196° Celsius, and can later be used for family planning using the Intracytoplasmic Sperm Injection (ICSI) method. So much for the theory.

Reading about scared the pants off me. I probably don't have to go into further detail about my thoughts at the idea that someone would cut my scrotum open and pierce my testicles with a needle. Was that really necessary? I weighed my options: 1. >> I go ahead with it and might have the opportunity to have biological children despite my azoospermia. 2. >> I don't do it and have no chance of conceiving biological children. With this in mind the decision was made within 10 seconds and I made an appointment in the andrological department of the University of Münster. At this first appointment my hormone levels were tested, a new spermogram was taken, an ultrasound of the testicles was made, the bone density was measured and a lot of paperwork was done. Afterwards I got an appointment for the TESE in 3 months.

Although I had been really hoping for a testosterone treatment for several weeks, I still had to wait awhile, because a testosterone treatment reduces the chances to find functional sperm by means of TESE. Well, a few more months with lowered testosterone levels didn't make any difference anymore.

Three months later the time had come. It is necessary that a guardian (family member, partner, friends) comes along and looks after the person for 24 hours after the operation. Together with my little sister I headed by car towards Münster. We had rented a small apartment near the surgery centre for 2 nights. On the day before the operation we had a 15-minute patient briefing with an anaesthetist about the upcoming general anaesthesia. Among other things, I was informed that a certain number of hours before the operation I was not allowed to eat or drink anymore.

Day of the operation: Beforehand I had been advised to remove my pubic hair on the morning of the operation in order to reduce the risk of infection. The day before, I had bought a depilatory cream for this purpose, which, contrary to expectations, worked extremely well. Now I was ready, and we drove to the operation center. For once, I did not hope for green

traffic lights, but was happy like a little child about every red light. No matter, we still arrived ahead of schedule for the operation. There we were welcomed warmly and I received a simple patient wristband with my name, date of birth and further information. In a changing room I was assigned a clothes locker, undressed completely and put on (as previously instructed) some green net underpants. Then I pressed a button to tell the care team that I had changed. Immediately a very friendly male nurse came and picked me up with a bed and covered me with several blankets. Already at this point I was given a painkiller so that I wouldn't have so much pain after the operation. Afterwards I lay on the bed for about 5 minutes in the corridor until I was pushed into the operating theatre. Here the last arrangements were made. The atmosphere was professional and friendly. Everyone introduced themselves by name and job title, which was very important for me. A peripheral vein access was placed in my elbow. This took a few seconds and was not painful. Then I received a breathing mask placed over my mouth and nose and was asked to count up to ten.

Three hours later I woke up in a large room flooded with light. That was it? Amazing! I hadn't felt a thing. I felt good and had no pain. I looked down to check if everything was still there. But my testicles were in a bandage and felt a little numb. Immediately someone brought me something to drink and a few biscuits. After half an hour of television I dared to go to the toilet. When I was back from the bathroom the doctor in charge appeared and after a short conversation I was dismissed. I was happy and amazed that I hadn't noticed anything at all during the operation. I realized that all the fears and worries I had about TESE were groundless. Still a little dazed, I went back to the waiting area where my sister was waiting for me. In the following hours I lay on the sofa watching TV and cooling my testicles with frozen peas wrapped in tea towels. The doctor had given us this advice and it worked well. The whole day I was still a little dazed by the anaesthesia, but on the whole I was fine and I had hardly any pain. I was able to sleep the whole night without any problems and on the following day I presented myself with legs apart for a check-up in the andrology department. There

the bandage was removed and everything was checked. Afterwards I was on sick leave for one week. I spent the next four days with my parents. I lay in bed a lot and recovered from the operation. Taking painkillers the pain was bearable. Finally, after a waiting period of 6 months since diagnosis, I was allowed to start the testosterone treatment. A few days later I received the joyful news that some sperm had been found by TESE and would now be cryopreserved. It took a load off my mind. All the effort had been worth it.

## The First Dental Braces are Due

On his first visit to the dentist my son was 3 1/2 years old. It was more by chance than intention that during this visit it was discovered why my child had problems with speaking. His teeth were too far forward so that the tongue had no resistance when speaking. The first braces were due. Although you could not call them proper braces. Rather it was a kind of rubber splint that my son had to wear from time to time. Since the jaws of small children are still very soft, his teeth were moved back slightly as if by magic. This treatment did not last long. From day to day, however, my child spoke more.

However it was already apparent at that age that his teeth were weak. The enamel was much too soft, which led to tooth decay despite regular brushing. Sealing them helped protect the enamel, but not permanently. Nevertheless, it happened that teeth simply "crumbled" despite being in dental care and regular half-yearly check-up. The decayed milk teeth were not extracted because this could only have been done under anaesthesia. It was assumed that if the tooth was extracted, it would disintegrate and the remaining root/broken tooth would have to be removed. The second teeth eliminated the "problem". They simply pushed the broken teeth away.

Now aged nearly 10 my son has got a "real", removable brace, because the second teeth are standing quite crosswise and the jaw is too narrow for the complete set of teeth. It is controversial among orthodontists to start

treating malocclusions at this age. Of course you don't want to "plague" the little ones too early with braces, leading to them not wanting to wear them anymore at some point. Our orthodontist consulted with our dentist and we jointly decided to take the risk of having braces at the age of 10. Regular check-ups (every 8 to 10 weeks) are carried out to see whether the brace is successful. In our case the brace is used to kill two birds with one stone. The jaw is slowly widened (for this the brace has to be extended at weekly intervals), and the teeth are "pressed" into an upright position.

So far we are pleased with the treatment. Of course my son doesn't like to wear the brace regularly either, but he knows what he's got it for. I think regular visits to the dentist are very important. I also had to learn to accept that it doesn't only depend on my son that he has tooth decay, but on the fact that his enamel is not the best. Once a week we strengthen the enamel with a special paste. The nice thing about it is that the paste has a slight Vanilla taste, which is of course very pleasant for children because it reminds them of ice cream.

I recommend to all parents: Pay attention to the teeth of your children! Not only in terms of dental health, but also if your sons don't start talking properly. Maybe you have the same problem as us.

### Matthias: My Life with the Syndrome

I am 36 years old, 1.98 m tall, at about 70 kg (up and down). Until I was 15 years old, I didn't know that I had Klinefelter syndrome. To what extent my physical ailments in my childhood had to do with Klinefelter syndrome can only be guessed today. As long as I can remember, I have always been ailing from childhood up to the present day. In the past I could not understand certain symptoms, which I know today had to do with Klinefelter syndrome. With the onset of puberty my weight dropped from 70 kg to less than 60 kg. I still remember well that even before that I had had enough after even the smallest portions of food and that this remained the case

for several hours. If I had already known then what I know today, I would certainly have been spared a lot. Even then I often had pain in my legs and knees.

My family doctor sent me to the university hospital in Frankfurt at that time. There I was tested for hours and was diagnosed with Klinefelter syndrome. I couldn't do anything with this information at the age of 15. I only knew that I now had to be injected every 6 weeks (250 mg depot). At that time I already weighed only approx. 60 kg. The endocrinologist told me that I would gain weight with the testosterone injections. This sentence never went out of my head, because I am still waiting to this day for this to happen. My body had thus adapted to the hormone. My maximum weight 3 years ago was 63.5 kg, but it always went up and down. As soon as the effect of the injection diminished, my weight also dropped. At that time I did not know yet that there was such a significant connection between the injection and the weight. I tried to eat more caloric food, but I did not gain weight.

But over the years, the effect of the depot injection no longer lasted six weeks, but shortened to seven to ten days. I asked my endocrinologist about alternatives to the depot injection and he recommended initially 62.5 mg testogel. I tested it, but the dosage was far too low. I noticed an enormous lack of strength after only a few days and switched back to the 250 mg depot injection. My endocrinologist then gave me double the dose, 125 mg in gel. He advised me to apply one sachet a day to my skin. In the beginning I was fine until I suddenly noticed that I could no longer hold my weight. It fell from 63 to 59 kg. I was nauseous and had lost my appetite. At that time I could not cope with the symptoms. My weight decreased from week to week and I felt worse and worse, but I didn't know that there was a connection between my bad condition and the gel. I voluntarily went to the HG Naturklinik (naturopathic clinic) in Michelrieth, where I was given infusions to regain my strength. During my ten day stay in the clinic I had chills, especially at night. I also suffered severe weakness in arms and

legs, muscle pain, and at times I was too weak to climb stairs. I had so little appetite that I could only eat in stages. My weight remained at 55 kg, at a height of 1.98 m. During my stay in the clinic I continued to apply 1x Testotop Gel 125 mg per day.

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After ten days I left the clinic. I was exhausted, I could have cried all the time, I didn't know anymore what the world was coming to. I then gave myself the depot injection once a week and continued to apply Testotop 125 mg once a day. It took me almost six months to regain some strength and increase my weight to 59 kg. Since this incident I am aware of the fact that testosterone has a big effect on my body, my well-being, my weight and my appetite. I travelled to all the endocrinologists in the Rhine-Main area to present my case, but I wasn't listened to. I was repeatedly reminded that there was no correlation between testosterone levels and weight. I sometimes even had to hear that I was only imagining everything.

From May 2013 to September 2015 I was able to increase my weight to about 70 kg. I felt good despite sports (active strength training and dancing). Until at the beginning of November I noticed that something was wrong again. Repeatedly I again suffered from mild symptoms like exhaustion and muscle aches, although I had been able to cope well with injections and gels since 2013. Unfortunately these symptoms became worse and worse, so that I was losing about 90 percent of my performance within two days. I looked for explanations and found none. Then I turned to Franz Schorpp and told him about my dilemma. The next day he sent me a report from Prof. Zitzmann explaining that certain foods can make testosterone levels drop. This was a real eye opener. There I read that garlic, ginger, liquorice and St. John's wort can do this. Ginger was the culprit. About six weeks previously I had had a long-lasting cold and had at first boiled the pure ginger root as tea, but later, to improve my cold symptoms, I had taken ginger root extract. Several times a day.

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I had never thought there could be a connection. My sense of well-being level was no longer present, I had the same symptoms as the two previous years, but now I knew how to deal with it. My weight dropped from 70 kg to 66.5 kg within a very short time. Once again I had severe nausea, loss of appetite and muscle cramps all over my body for several days at a time. I tried to relieve my symptoms with magnesium, but it didn't help at all. So I had no choice but to administer the depot injection once a week again, plus two sachets of Testotop 125 mg. In the first days I had the impression that the effect of the injection had already depleted after three days. My sport activities and especially my dancing sport had come to a complete standstill, I simply had no strength left, I even had to stop working. I was extremely depressed again, also my nerves were frayed again, I would have a crying fit at the slightest sad thought.

Now after about three weeks I can say that I have climbed out of the valley again. I feel better, my strength is almost 100% restored, I am not losing weight anymore. Gaining weight will be again a tedious process. I once again have made an appointment at the UKM (University Clinic) Münster with Prof. Zitzmann to have myself tested for androgen receptors, as the 250 mg depot injection or Testotop alone is not sufficient for me to feel well.

How do I live with Klinefelter syndrome? I would say relatively normal today, like everyone else. In retrospect, it was lucky that Testotop didn't work with me, because otherwise I would never have noticed that there is such a strong connection between the level of testosterone and my weight and appetite. I may not have been the fastest at school in terms of comprehension, but I struggled my way through to the Abitur (high school graduation) and completed my studies in communications engineering with a good grade point average. Since then, as an independent IT specialist, I have been a contact person for companies and private customers. In my private life I am still single. This may be due to my shyness towards women. That's why I try to work hard by cultivating my contacts with women

in the field of dancing. Dancing sport has become so important in my life that I can no longer do without it. I notice above all that my performance increases very slowly. I have gained some muscle, but by no means as much as other athletes.

### I'm the Mother of a 24-Year-Old Boy

Klinefelter syndrome was diagnosed while I was pregnant. The only thing the doctors did was to send me to an endocrinological consultant because Klinefelter syndrome is subject to abortion law here in Germany. The only information I got was that the child will look normal and that there is not much information about the development of these children. Some would have problems at school, others would not. I should go for an endocrinological examination with him from time to time.

I wanted my baby! Max doesn't want to know too much about Klinefelter syndrome right now. We have had hard times. Sometimes I wondered how I could keep going on as a single mother. The father still does not accept the diagnosis.

Max is not fond of groups, and he is very loyal to friends. He has a very good feeling for ball games like tennis, golf and basketball. He makes it look so easy. But he doesn't use his talent. He is talented in painting and music. Unfortunately he doesn't want to use this potential in a profession yet. School was terrible. He only began reading when he was 13, but he is very good at visual learning. Our school system was not the best one for him. He is very emotional and sensitive. He has an active sex life. He dreams of love, family and children. He has a wonderful personality. Finally he has decided on his career path. He is doing an apprenticeship in sales, because he likes to deal with people of all kinds. He was always tired, inactive and could not really concentrate, so I tried to find a way to support him.

For five years he has been helping his body daily with highly concentrated micro-nutrition. His energy level is good. We have also changed our diet. No white sugar, only high quality fats, less carbohydrates, fruit, salads and high quality proteins. So far, we've been doing without testosterone boosters or chemical medications.

Can we blame the Klinefelter syndrome for all his difficulties? His testosterone level is just 4.9. The breast growth has disappeared again. Beard and body hair are growing normally. He is developing into an open person in our society. Max is now 1.95 meters tall and has a thin physique. I'm so proud to be an additional help to him.

### Bernhard: My Life with the Syndrome

My name is Bernhard, born in Munich in 1958 and still living there today. After school I trained as a bank clerk; after a few years I changed jobs and moved to the finance department of an industrial company. There I worked for several years in international contract financing focusing on securities and bank guarantees. Later I changed to accounting as a balance sheet and business accountant, my main tasks were in all areas of bookkeeping. I have successfully participated in projects such as the introduction of SAP/R3, the changeover to the euro, incorporating and selling off corporate business areas and have taken care of issues relating to deferred taxes, value added tax and withholding tax in the context of accounting and reporting as well as IT.

I received the diagnosis 47,XXY in 1991 during a visit to a fertility clinic.

In spring 2008, after extensive restructuring and job cuts, I left the company and wanted to contribute my knowledge and know-how elsewhere. This was initially very promising, but at the end of 2008 the financial crisis hit Germany, and I was not hired after the trial period. My job search turned out to be difficult during the financial crisis: I was either too expensive or

overqualified. When I then managed to get an employment contract again, it was difficult for me to integrate myself as a “newcomer”.

For a long time I considered the typical testosterone deficiency symptoms to be the cause of my difficulties, and so doing research on Asperger, a highly functional autism with similar symptoms, was no longer my first priority. In 2017 I visited the outpatient clinic for Social Interaction at the Max-Planck-Institute (MPI) in Munich under Dr. Leonhard Schilbach<sup>1</sup>. In January 2018, after visiting the MPI day care unit, I received the diagnosis and applied for early retirement, which was approved without any problems. The fact that I am affected by both conditions has already brought relief to me; the hitherto unanswered questions about the connections between Klinefelter and autism, addiction, ADHD and other diagnoses complete the puzzle and can be found in the following text.

## I Can't Deny Myself: Autist Blogging – Klinefelter

Some Klinefelter carriers do not want Klinefelter to be associated with anything other than Klinefelter, even though scientists sometimes refer to the second X chromosome as a gender development disorder. For them even correlations with ADHD or autism are unthinkable, although there are more overlaps than opposites. Autistic people, too, sometimes want to set boundaries. Some want to separate Asperger from autism, while others want to separate Asperger from other genetic syndromes. You hear statements such as: “The cause is unknown! There is no overlap. This dilutes everything.” Both groups, the autistic group and the Klinefelter group, are united by the conviction that their disposition or disability is a unique feature. I understand the desire for clarity, and I would have saved myself years of uncertainty and suffering if genetics and everyday problems could be assigned more clearly. Basically, my first diagnosis XXY also ensures me that the second diagnosis Asperger is correct, because so many symptoms overlap. The researchers may argue among themselves as to whether the symptoms have different causes. But I still see myself in the stories of

other autistic people. And the enormous response to earlier blog posts showed that many autistic people see themselves in my descriptions as a Klinefelter autist.

## Diagnoses and their origins

We know so very little about the causes of autism. Autism diagnosis in conventional practice is pure observation of behaviour! Check off a few points on the checklist, observe, test and that's the diagnosis. We know little about genetic causes, and even more contradictions arise in neurological tests. Klinefelter is set at 47, XXY. This is a genetic diagnosis. The spectrum is so wide, because an incredible amount of information is stored in an additional X chromosome, but a whim of nature decides (from today's point of view), what of it actively influences the phenotype. The Klinefelter phenotype was discovered in 1942 (but it was not until 1951 that the genetic cause was found), autism was medically researched by Kanner and Asperger around the same time. Both diagnoses developed independently until the turn of the millennium, because Klinefelter was long understood as a predominantly physical diagnosis. It was assumed that the cause for the phenotype was testosterone deficiency. Only in the last ten to 15 years has the number of studies investigating the influence of the additional X chromosome increased. In addition, the first studies on testosterone therapy did not meet common quality standards (placebo, double-blind, long-term study). There are now even doubts as to whether testosterone therapy can really prevent or reduce osteoporosis, diabetes and other concomitant diseases.

## Klinefelter and psyche

Not much was known about the psyche of Klinefelter patients for a long time. Most of the effects were attributed to testosterone deficiency and its consequences, for example non-specific symptoms such as listlessness, fatigue, passivity, depression or probably the most serious effect, infertility. For decades, it was considered certain that testosterone treatment was the standard method following a Klinefelter diagnosis. The inherent expecta-

tion is that fatigue, depressive mood and listlessness disappear as soon as testosterone is injected or applied via gel. This is why double-blind studies are so important, i. e. not only the administration of a placebo, but that not even the treating physician knows whether he has prescribed testosterone or a placebo. This also prevents the subjective expectations of the doctor from influencing the result. My experience and that of Klinefelter carriers I know is that most attending physicians consider testosterone to be the standard therapy and also attribute symptom improvements to it. Little is said about other psychological effects. The doctor is a urologist, endocrinologist or andrologist, not a psychiatrist. There is hardly any interdisciplinary exchange. This is my biggest point of criticism. People with Klinefelter syndrome need holistic care. Testosterone therapy is part of this, psychological support is another part. An andrologist should at least know what else can be included in Klinefelter's overall package. When I was given human genetic counselling at the University Hospital of Innsbruck in 2008, the psyche was not once mentioned. I would have saved myself a lot of suffering and setbacks if I had been told at that time that autistic behaviour patterns frequently occur in the Klinefelter phenotype. I probably would have started researching more about autism at that time - curious as I am - and would have been able to better understand some problematic situations. Instead, I got to know other Klinefelter carriers, hardly recognized myself in their behaviour, and distanced myself mentally from being one of them.

I recognized myself to be an unusual case that didn't fit in anywhere properly and hardly dealt with it in the following years. If you have a rare disease or a rare syndrome, there is little talk about it in public. The public is comparatively well informed about autism, but not at all about Klinefelter. It is also much easier to come out as an autistic person because autism has purely psychological abnormalities (apart from motor skills), while Klinefelter affected persons sometimes have to put up with shameful questions about the size of their genitals, secondary sexual characteristics or their unfulfilled desire to have children. A partial outing is difficult,

thanks to Wikipedia and other platforms with their detailed focus on physical characteristics/defects. However, I personally don't define myself through my body.

### Overlaps

Back to the source. There are overlaps with other diseases (Autism is not a disease for me. Unfortunately I cannot change medical terms, and autism is considered a disease here.). Accompanying symptom or causal effect? Of course, this question always arises. Does a mere accumulation of an accompanying symptom mean a causal connection? Not necessarily. The cause of transgender is not XXY, but rather low testosterone levels, the female phenotype as well as the female X chromosome favour deviations from the male phenotype. Even if the majority feels and thinks male, it is not surprising if a minority does not feel and think male. The phenotype favours this.

This also favours an accumulation of autistic behaviour, both negative and positive. Klinefelter carriers are often described\* as follows (\* in self-help books, on club pages, in forums, etc.):

- >> very sensitive to sounds, sometimes also smells and touch
- >> highly sensitive or over-empathic
- >> often gross/fine motor problems
- >> problems in adopting the perspective of the other
- >> low frustration threshold, frequent meltdowns
- >> love of detail
- >> often a talent for visual / spatial perception (art, photography, drawing, engineering, mathematics, programming)
- >> ruthlessly honest, sometimes naive
- >> verbally not very communicative

Is this number of overlaps with autistic symptoms just a coincidence? They occur independent of age and testosterone, even before puberty, before



there are any differences to XY boys. Probably one of the main reasons why autism is less frequently diagnosed is the generally weaker symptoms in the area of special interests, stereotypes, rituals. However, the core symptoms are present (difficulties in communication and interaction).

The Venn diagrams (left) illustrate the overlaps. The graphic below was taken from a publication, the other one I made myself. They are neither complete nor exact, but are intended to show which multiple diagnoses can exist.

### Multiple hit theory

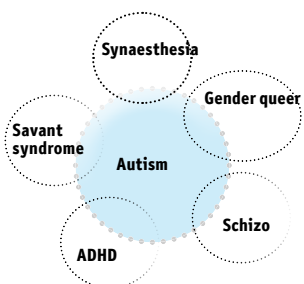
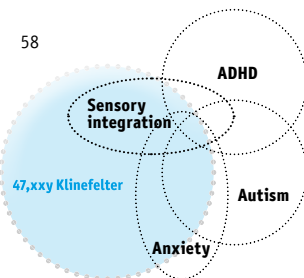
So is Klinefelter merely autism with low testosterone levels?

It cannot be simplified in this way, however, because the studies also show that around one third to one half do not receive an autism diagnosis. The study on the presence of CNVs (Copy Number Variations) could provide an explanation for this, namely that it depends on which and how many DNA segments are duplicated in the second X chromosome. This is also consistent with the multiple hit theory on autism that states several “risk” genes have to come together before autism is generated (and again it gets complicated because autism is not a single feature but consists of many different features). So it seems that some Klinefelter carriers are protected against autism because they do not have these CNVs.

### Exclusion diagnosis?

Critics of my views like to point to a lecture in which Klinefelter is seen as an exclusion diagnosis for autism.

„In childhood, KS boys sometimes stand out for a behaviour that is generally referred to as autistic behaviour, but which has to be differentiated from the disease pattern of autism. This behaviour is primarily characterized by withdrawal, less interest in interacting with peers, and a particular passion for detail.“



Why is it imperative to draw a line here? If the behaviour is strongly autistic, can all criteria for an ASD diagnosis be present. Unfortunately a perception for detail also has a negative effect due to an increase in impaired stimulus filtering. I know affected persons, including myself, who suffer primarily from background noises, increased odour perception and sometimes distraction through movements, but have also developed strengths, such as special interests. However, I agree with you that presumably “only” social communication is impaired in most cases, and routines/special interests occur rather rarely, at least according to Bruining H. et al., Psychiatric Characteristics in a self-selected sample of boys with Klinefelter Syndrome, Pediatrics, 2009. The crucial question is probably: Is a double diagnosis of Klinefelter and autism possible? A look at various studies shows: Yes. In the Netherlands about 30 percent receive an ASD diagnosis, in Sweden autism occurs six times more frequently in Klinefelter than in the general population. In my opinion, a differentiation would be necessary if the autistic symptoms could be reversed by a causal treatment of the genetic syndrome, i.e. by testosterone treatment. However, there is no evidence of this.

For me the second diagnosis Asperger meant a considerable progress in my quality of life, a plus in support, a gain in knowledge regarding the past and present, more thoughtfulness, attentiveness, but also serenity for the future. Why should I have been denied this because of arbitrary limits?

### What matters is what helps – not what it’s called

One last point: What matters is not the name of the diagnosis, but what helps me. The diagnosis could also be called cabbage sprouts, hare or Tabalugaland. As an average person affected, I am not interested in the academic babble, but rather: What helps me in my everyday life? How do I get my life on track? How can I live as autonomously as possible and become financially independent?

So I have helped myself by following and copying the tips and tricks from autistic people, long before I received the official diagnosis. Regardless of

its name, it is obvious that someone with impaired stimulus filtering cannot get accustomed to an over-irritation. Whereas I had thought before, I must only expose myself often enough, then I will get used to it, like everyone else – what actually helps is to avoid overburdening situations or take enough breaks. This indeed works regardless of whether the diagnosis is autism or here. I am convinced that it doesn't hurt anyone to copy helpful tips from others.

No autistic person is denied the need for support if a non-autistic person suddenly takes action armed with earplugs and sunglasses against sensory overload. Also no ADHD affected person will suffer damage if I copy him and adopt more efficient to-do lists. Things like disadvantage compensations are only granted with an official (disability) permit anyway. As long as Klinefelter is still unknown, however, those affected sometimes need a permit for autism in order to receive the same support as autistic people without Klinefelter.

**Reading recommendation** Allen Frances – *Normal. Gegen die Inflation psychiatrischer Diagnosen (Against the inflation of psychiatric diagnoses)*. DuMont Buchverlag, 2013 – It is also helpful to find causes if additional therapy/medication becomes necessary. Or if autistic symptoms show a degenerative course (e. g. Rett syndrome).

### **Differentiation also makes sense**

Of course differentiation is useful when it comes to medication, for example. Ritalin is useful for ADHD, but sometimes counterproductive when there are other causes of attention deficits, such as chronic depression.

I don't like to make generalizations – I neither suggest to refrain from differentiations, nor to put everything into strict categories. Nature has no strict boundaries. My concern is to broaden horizons, to allow that nothing is that clear, and that medical research continues to develop. Considering that research into the high stimulus sensitivity of autistic people has only

been going on for about five to ten years, we still have many discoveries to make. Source: [autistenbloggen.wordpress.com/2016/04/04/ich-kann-mich-nicht-verleugnen](https://autistenbloggen.wordpress.com/2016/04/04/ich-kann-mich-nicht-verleugnen)

## **Stigmatisation of Boys with Klinefelter Syndrome at School**

Stigmatisation refers to a process in the course of which, within a group, certain characteristics, for example a disability, are assigned negative ratings and the individuals concerned are pushed into a marginal group position. Stigmatised people are thus primarily perceived via negative characteristics. Other positive characteristics cannot compensate for this stigma. This means that the environment of a child ascribes a certain role or position to it, for example in the class group. The child is assigned very specific behaviours. Even if the child no longer shows these noticeable features, it retains its "stamp". This phenomenon can be caused particularly by so-called fashion diagnoses such as AD(H)D or exceptional giftedness. We recommend to be careful with such terms. Only a psychologist can make a diagnosis after thorough testing. In any case, it is advisable for the parent to be as relaxed as possible with the new situation after school enrolment. Get to know the teacher and then decide.

**Leon starts school** – Klinefelter boy Leon starts school this year. In kindergarten he often showed great difficulties in social interactions and reacted impulsively and aggressively to conflicts. Although he was able to stop this behaviour, he is often very restless and can only concentrate for a short time. It could now happen that the teacher starts stigmatizing Leon after talking to his mother about his background. She now pays close attention to his behaviour. If he in the beginning of his school days is hardly able to sit quietly on the chair, this is already the first confirmation for the teacher. If conflicts arise in which Leon is involved, the teacher might ascribe to him exactly the negative qualities described by his mother. Leon is ascribed the role of troublemaker by her.

But it could also be quite different. The mother tells the teacher about his difficulties. The teacher then specifically selects a low-stimulus seat and seats him beside a calmer boy who has a positive effect on Leon. In conflicts the teacher can still support Leon at first, until he has integrated himself well into the class. If Mrs. S. does not tell the teacher about the prehistory, it can well be that Leon adjusts his way quickly to the school situation. Meaning he has a lot of fun and that concentration difficulties don't start in the first place.

### How Do I React When my Child is Bullied in School?

Just like at work, bullying is widespread at school. Since bullying victims usually cannot defend themselves, they need external help. To do this they have to confide in a trusted person – parents, friends, employees of a counselling centre or a guidance teacher.

#### Bullying as a symptom of disturbed communication

The victims are isolated, the offenders receive no feedback about the effects of their harassment. The uninvolved classmates suffer from their neutral position. They have no courage to inform teachers or parents about the incident, for fear of becoming a victim themselves.

#### Symptoms and consequences of bullying

- » ruminative thought processes, such as memory disorders, concentration difficulties, depression, apathy, lack of initiative, irritability, helplessness, aggression, feelings of insecurity, oversensitivity
- » psychosomatic symptoms such as nightmares, abdominal pain, stomach pain, diarrhea, vomiting, nausea, loss of appetite, lump in throat, crying, loneliness, lack of contact
- » fright symptoms such as chest pressure, sweating, dry mouth, palpitations, shortness of breath with asthma, blood flushes
- » Pain of the back, neck and muscles
- » Sleep disturbances

#### How parents should deal with bullying:

- » If your child confides to you that he or she is being bullied at school, you should listen to him or her and trust him or her. Avoid, however, making the subject the number one topic of conversation.
- » Do not reproach or blame your child. Believe his statements and assure him of all kinds of help and support.
- » Please do not contact the offender's parents. This can only aggravate the situation. If the offender's parents punish their child, this often has an effect on the victim – the offender takes revenge on the victim.
- » You shouldn't contact the offender either. This will weaken your child's position. Offenders and other classmates will think that your child is not able to defend itself on its own.
- » Do not take your child along to the conversations with the teacher.

In principle, it is worth making the incident public and getting in touch with other parents. In many cases bullying victims are not single victims. The bullying has nothing to do with the victim's personality characteristics, but is part of the system of the school concerned. A change of school might produce relief.

### Annual Check-Up by the Medical Specialist

For Klinefelter patients it is absolutely necessary to consult a specialist (endocrinologist) at least once a year, better yet twice a year. It should be a matter of course for the attending physician to carry out the periodic check-ups. The following examinations are recommended in the package inserts of the current drugs (injections and gel):

Breast and prostate once a year. In the case of older Klinefelter patients carriers and patients with a special risk, twice a year. Furthermore, it is recommended to have a complete blood count, differential blood count, fat (lipid) profile and liver function test as well as the testosterone level in the blood determined.

In older patients, hormone treatment can lead to benign enlargement of

the prostate gland and thus to problems urinating. You should inform your attending physician if such difficulties occur.

Treatment with hormone preparations can also lead to water retention in the tissue (oedema). If this is the case, talk to your attending physician. Since diabetes occurs more frequently with Klinefelter syndrome (Prof. Zitzmann), the HbA1c level (long-term blood sugar) should also be monitored at the same time – as should the thyroid levels.

It is repeatedly pointed out that patients who are treated with hormones should also read the package insert according to the advertisement: “For risks and side effects ask your doctor or pharmacist”.

Every doctor is obliged to give his patient a doctor’s letter after an examination. This report is particularly important for further treatment by another specialist. Finally, blood donation should also be mentioned, since there is a widespread opinion that Klinefelter syndrome patients should not donate blood. This is not the case however.

Hormone treatment can cause increased blood formation (“thick” blood). This phenomenon can lead to heart attack, stroke and thrombosis, especially in older Klinefelter patients carriers. Regular blood donation can prevent this problem. The blood donation service has raised the participants’ ability to donate up to the age of 72. For all those who are no longer allowed to donate for age-related reasons, there is another possibility: bloodletting. It is almost the same as a blood donation, but the blood may not be used and must be disposed of. Every general practitioner or specialist can carry out bloodletting. It has no side effects unlike drugs that are prescribed for blood thinning.

It is absolutely essential to diagnose Klinefelter syndrome at an early stage, preferably at the beginning of puberty, in order to avoid possible late effects such as osteoporosis, reduced quality of life, diabetes and obesity.

## High Sensitivity

While more and more adults with this disposition eventually learn to accept and value themselves and to feel liberated, the gained awareness of the topic gives us the opportunity to accompany our sensitive children right from the start in a healthy way. The line between overprotection and counterproductive “hardening” is narrow. If the child is moreover a highly sensitive person – which, according to current knowledge, applies to 20 percent of people – this balancing act can be not only exhausting, but even stressful. Since it is a neuronal disposition and not a disease, disorder or disability, there is no diagnosis. There are many tests that serve as orientation, but you don’t get them in the classic “black and white” way. The mere fact that there are so many facets of sensitivity (from olfactory to tactile to acoustic emotional) makes a standardized test almost impossible.

The first signs of a highly sensitive disposition can be found by looking at the parents. High sensitivity is inherited. Even during pregnancy there could be indications of a sensitive child developing. Even in the womb a startle could possibly be noticed. Once the highly sensitive child is born, it may (but does not have to) be that the offspring is overexcited more quickly, be it through unusual situations, noise, touching, moods, smells and speed.

## Make children fit for life, but at the same time protect them from overstimulation

Parents of a highly sensitive child who want to prevent it from this sensory overload are often told that they are being overprotective. Just as the seemingly well-meant sentence “You have to toughen the child up sometimes” becomes a torture in the long run. But how can this balancing act be accomplished? There is actually one piece of advice on bringing up children, and it is called “gut feeling”.

Intuition helps in finding the correct handling of highly sensitive children. The first question to ask is which direction one as a parent tends to go. This

tendency often has to do with the parent's own childhood experiences. It would be extreme if a parent had bad experiences with his or her own sensitivity and is now forcing a toughening up à la "don't be such a baby!". The other extreme would be total overprotection and an avoidance attitude towards the demands of daily life.

There is a clear need for differentiation: Which challenges are necessary, support the child, bring it forward? Which ones however are avoidable because they burden and weaken? Avoid unnecessary stressors for children with high sensitivity: The latter have a lot to do with social structures and standards. It is certainly half the battle to get rid of them or to reflect on them critically. Does the highly sensitive son really have to join the art club? Is it helpful and confidence strengthening that the introverted, highly sensitive child is brought to the halfpipe with the longboard, so that he becomes like other boys? To what extent does it help the boy in his personality development if he is not allowed to cut the scratchy labels out of his sweater?

But in the long run protecting the child from all stressors is not in the interest of every child. The challenge here is to gently introduce and expand the requirements. A classic example would be giving a presentation to the school class. This is unavoidable, and even in the course of adult life there will always be situations in which it is important to speak for oneself or for a cause in front of other people. In this particular example, it might be a good idea to practice in advance. For example the child could present short texts, explain things or read stories in the weeks before the presentation, first to the parents and later to a wider circle of relatives.

Gut instinct is still the best guide in parenting. Of course, questioning this from time to time is also a good idea. Often children can do more than you initially think. Using intuition to consider how resilient your child is would be desirable. Have confidence in your child! Please be aware that excessive protection can also convey to the child that you do not have confidence in him.

The negatively connotated "helicopter parents" is usually associated with this. "To helicopter" is not wrong at all. After all, it means being nearby when needed. For the sake of your child, make sure that the helicopter circles are wide enough so that they are not monitoring, noisy and disruptive.

## Going With and Learning from Each Other



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#lebenmit47xxy

**On this page we would like to introduce a new website, which was recently started by one of our members.**

My name is Jakob. I have been a member of the association 47xxy for a year now. It is great to be surrounded by people who want to make changes and be able to inform and support people with Klinefelter syndrome and their relatives on a daily basis. As a contribution to this wonderful community, I have recently launched a website. There you can find a lot of information about Klinefelter Syndrome including information about contact points and doctors. Under the heading "Neuigkeiten" ("News") you will find current newspaper articles or new scientific findings. There are links to videos and much more to discover. Just have a look! If you have questions or suggestions, you are welcome to contact me. See you, Jakob



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