**Prader-Willi-Syndrome: genetic cause, characteristic features and therapeutic options**

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Prader-Willi-Syndrome is one of the so-called rare diseases although with an incidence of 1:10.000 to 1:16.000 lifebirths it is not that rare. Its genetic cause is a missing part on the long arm of chromosome 15 and it is always the paternal allel which is missing. I am sorry that this picture is in German but I think it is easy to understand for all of you. In most cases there is a deletion, but also a uniparenteral disomia can be the reason, which means that the paternal allel is missing and the maternal one is duplicated. Moreover it can appear as an imprinting disorder, where the DNA of the paternal allel is methylated in the maternal way and so also the genes are expressed that way. In rare cases there are balanced translocations to other chromosomes.
Here is the relevant area of chromosome 15. As you can see, it contains at least 14 genes. Yet we do not know their concrete relevance for the special features of Prader Willi syndrome.

But before you can make the diagnosis of Prader Willi Syndrome by performing genetic testing, of course, you have to recognize the characteristic phenotypical features of the children, which in this syndrome also show typical changes during the course of life.
As you can see on these pictures, in the neonatal period the children look quite different from what you know of older Prader-Willi-children. Often mothers report already on reduced fetal movements. The children are frequently born preterm and have a low birth weight and length. Actually they are rather only below the 25$^{th}$ percentile and no real SGA-children who would be below the 3$^{rd}$ percentile. Head circumference is normal. The most impressive symptom of the newborns is their extreme muscular weakness. They are the classical floppy infants, show few movements, a weak cry and are almost unable to suck or drink. Because of their severe feeding problems all of them need a gastric tube, often for the first weeks or even months of life.
When you look into the faces of the children you also recognize several dysmorphic stigmata: The children have al long, narrow forehead with a large fontanella which goes down far into the front. I am sorry that I cannot show you the characteristic almond shaped eyes for reasons of anonymity of the children, but you see the small triangular mouth which is nearly always open, also in later years. Starting from the beginning, the children also have a very characteristic extremely sticky saliva. Often you can see a marmorated skin. Moreover most children show a genital hypoplasia. In girls both labiae maiorae and minorae are hypoplastic, in boys it is the scrotum. Boys also usually have a cryptorchism which shows no spontaneous descensus or response to hormonal treatment, so in almost all of them surgical orchidopexy is necessary.
Here you see another example of the characteristic face and I would ask you to remember this little girl who is the same as the newborn you saw before. On the other side there is an example of the genital hypoplasia of a girl, because of which you look almost directly on the vagina.

In childhood and adolescence you still see the typical face and the soft skin and I think you can imagine the general hypotonia, which persists in later life, even by seeing only the faces of these two boys. But in contrast to the first year of life, children now show a severe weight gain. Here is another example of the open mouth with the sticky saliva und here you see the very small hands and feet which I have not mentioned yet.
On this picture now you see the complete phenotype as this girl was diagnosed only at the age of 12 years and so received no treatment. She shows the classical morbid obesity of Prader-Willy-Syndrome, especially of waist, hips and upper legs. Compared to this the hands and feet appear even smaller. Children and adults have a short stature, in 75 % there is a scoliosis which often starts already before the age of 5 years. Frequently, but not obligatory there is a hypopigmentation of skin and hair at least compared to the individual family members.

By knowing the special features now, I think you can already guess quite a few of the medical aspects we have to care for in children with Prader-Willi-Syndrom. There are several endocrinologic problems, of course there are the hyperphagia and obesity and finally I will say some words about the developmental and behavioural problems of the children.

Concerning endocrinologic aspects, usually the short stature of the Prader-Willi-children is noted first. On these diagrams, the grey area represents the percentiles of normal growing boys respectively girs, the lines show the percentiles of Prader-Willi-Syndrome children. So boys end with a final height of about 159 cm in the mean, in girls it is below 150 cm. Another characteristic feature which is shown quite impressively by the comparison in these diagrams is the missing of the pubertal growth spurt in Prader-Willi-Syndrome.
To improve final height of children with Prader-Willi-Syndrome, growth hormone therapy has been tried and shows effects. There are still ongoing debates if it should be used in all children with Prader-Willi-Syndrome or only in those who also have growth hormone deficiency. There exists a real growth hormone deficiency in Prader Willi syndrome and it is more common than in normal population. Diagnosis is made by auxology as these children are not only small but show also a subnormal growth velocity, that is they grow not only continuously below the 3$^{rd}$ percentile but as you can see here for this still quite young girl, fall out of their own percentile as we call it. Regarding laboratory values, IGF-I and IGFBP3 are low. Stimulation tests which are normally used for diagnosing growth hormone deficiency are not indicated in Prader Willi Syndrome as they show very varying results and so are not reliable.
Growth hormone therapy not only improves longitudinal growth but has also other positive effects in Prader-Willi-children: Treated children also show better energy expenditure, more physical strength and even an improvement in cognitive abilities. But on the other hand, there are special concerns on GH therapy in PWS children. Because of them and the better effects in them, we and many others treat only the really growth hormone deficient children. While not seen in other growth hormone deficient children, quite a large number of deaths during growth

hormone therapy are reported in PWS-children with a clustering during the first months of treatment. The suspected reason is that the increase of IGF-I induces hyperplasia of tonsils and adenoidea which, combined with the hypotonia of the tongue and thepharyngeal muscles can cause apnoeas. Especially when children additionally suffer from an infection, they can become so severe that they might lead to death. That is why morbid obesity as well as apnoea in polysomnographia are strict contraindications for GH-therapy in PWS children. Performing a polysomnographia is obligatory before start of GH-treatment in PWS children and controls during therapy should be done either routinely or at least when parents report that their children start snoring.
Here is a young boy treated with growth hormone and diet, about which I will talk later. As you see, he looks quite different from the youths I showed you before. Yet, here you also see a good example of the scoliosis which usually is not worsened or induced by the growth hormone.

Another endocrinologic problem of PWS children is the frequent development of hypothyreosis. Please note that it is a central hypothyreosis although TSH is not that low as you know it from classical hypopituitarism. You would rather expect laboratory findings like this with only moderately lowered TSH, fT4 and fT3. But already this constellation is an indication for L-thyroxine treatment. As usual in central hypothyreosis, fT4 and fT3 but not TSH are the relevant parameters for surveillance.

In adolescence the next appearing problem is the onset of puberty. It is usually delayed in PWS children. In rarer cases its start is normal but pubertal development always stays incomplete. It is quite amazing that in PWS children hypogonadism can be central, usually seen in the girls, but also primary, which is the main form in boys. Men with PWS normally reach a testes volume of only about 7 ml (in normal men: 20-25 ml) and a testosterone level of maximal 150 ng/dl (compared to 500 or more in normal men). They have a high FSH and inhibin B often is not measurable which signals missing spermatogenesis and actually all men with PWS are infertile.
In girls, spontaneous menarche appears in about 40 percent and sometimes is achieved only at 20 years of age. I have to mention that these are older data as today usually a hormone substitution with estrogen respectively testosterone is given to the children to induce puberty at a normal age. As there are 2 reported pregnancies in women with PWS, infertility seems to be frequent but not obligate in them
Here you see an example of the appearance of a young girl who had the full endocrinologic treated with growth hormone, L-thyroxin and estradiol.

The most well-known characteristic of PWS children, of course, is their hyperphagia and consecutive obesity. Hyperphagia begins at an age of 3-4 years: The children then show excessive food-seeking behaviour, they are always hungry, continuously ask for food, search for food, eat

everything they find. Although calory-rich and sweet or fatty food is preferred, they would not hesitate to eat food out of the garbage. Weight gain is additionally increased by the children`s abnormal body composition with reduced lean and increased fat body mass compared to normal as well obese controls. This is supposed to be also the reason for their reduced energy expenditure.
The pathophysiological explanation for the missing feeling of satiety in Prader Willi syndrome seems to be a hypoplastic nucleus paraventricularis going along with a reduced number of oxytocin-producing neurons. Oxytocin is a satiety hormone whereas ghrelin, an appetite stimulator, is increased. Pancreatic polypeptide, which also signals satiety is low, too. This girl represents the classical phenotype of PWS with the typical features of excessive central obesity.
In PWS children there is a high risk also for unusual complications of the excessive obesity because of special other findings: PWS children have a decreased ability to vomit and an increased tolerance of pain. So they might for example eat also higher amounts of spoiled food, they tend to binge-eating which can lead to choking episodes. These are a quite frequent reason for death in people with Prader-Willi-Syndrome. Moreover gastric emptying is prolonged so together with the binge-eating there is the danger for gastric necrosis and perforation and additionally for delayed diagnosis because of the missing symptoms. So everybody in medical charge for PWS children should be aware that vomiting and abdominal pain is a real alarming signal in them and we also have to instruct parents to recognize this.
Other complications are, of course, the morbid obesity itself, a diabetes mellitus type 2 which is seen in about 25 % of even young people with a BMI above the 95$^{th}$ percentile, sleep apnoea, which I already mentioned and the development of a Cor pulmonale in adults. But, which is quite astonishing, apart from the diabetes, people with PWS do not develop the classical features of a metabolic syndrome. Why, we don`t know.

Of course, treatment options for obesity and hyperphagia in PWS are urgently searched for. Yet, all the pharmacological trials with diverse agents did not show any significant effect. But there is an option which is successful is a very strict and early starting diet. This sounds to be simple at the first glance, but I tell you, it is not. This diet does not only have to be low in calories and must be low in fat and in relation to that high in proteins. The early start before the onset of hyperphagia is very important. In spite of the feeding problems in the first year of life a fast gain of weight should be avoided even then and diet should start at the end of the first or at the beginning of the second year, so actually just when parents are happy that their child finally eats after having fed it with the gastric tube for a long time. And be aware: it is a really, really hard job for the parents and caregivers. They have to be extremely consequent with their children and survey them in every second to prevent them from searching for food. To show you the outcome of the diet I first wanted to show tables of study results for weight, BMI and so on, which of course exist. But then I decided to simply present to you these two children: Here the un-

treated girl you already saw before and on the other side a boy treated with diet and growth hormone since early age. I hope you agree with me that the difference is really impressive.

Finally let us have a look at motoric and mental development of the Prader-Willi-Syndrome-children. Achievement of motoric milestones is usually delayed, in part certainly caused by the hypotonia. For example, at our clinic there is a boy who is 4 years now and still does not walk. So physiotherapy is often indicated in these children, often also because of the scoliosis. Mental development is impaired, too. The mean IQ of Prader-Willi-Syndrome-children is 63. There is a normal distribution so 5 % have a low-normal IQ, 5 % show a severe intellectual disability. Here we can see some differences: Children with maternal uniparental disomy show better speech and better adapted behaviour while children with a deletion have better visomotoric abilities.

Combined with the intellectual deficits there are severe behavioural problems: About 20 % show autistic symptoms like stereotypes and rituals, starting from early age, there are frequent temper outbursts, impulsivity and emotional instability. The children show obsessive behaviour, especially skin picking which I will show you on the next file as well as other aggressive and selfaggressive symptoms. In later life, criminality is not rare, mainly in the form of stealing food. Moreover there is an increased incidence for narcolepsy and cataplexy as the missing of oxytocin is known as relevant in narcolepsy, too. Options for treatment are actually not really satisfying. Of course, instruction of parents and caregivers are important who have to set up clear and consequent rules not only for eating but also for behaviour. Not seldom help of psychologists and psychiatrists is needed. Medical options are risperidone, which often shows quite good effect or SSRIs, especially fluoxetine as antidepressant but also because of its negative effect on appetite which actually is small, if existing at all. One study found N-acetyl-cystein to be effective against the skin picking. I know that Siggi Kruse will also tell you about some other, maybe better possibilities

Here is the picture of skin picing: This terminus describes that if the children have any little skin lesion, they manipulate on it until it gets really deep and large, often with following infections and problematic healing.

In consequence of all this, social integration of people with Prader Willi syndromes is difficult. Children need adequate schools and in adulthood, PWS-people are almost never to live on their one. They usually need specialized living facilities with caregivers who know how to deal with the behavioural and eating disorders. According to data from the USA, 35 % have no work at all and only 46 % are on regular work but usually they do only helper`s jobs or other simple activities.

Finally, mortality is definitively increased in PWS-people. The main reasons for dying are gastronintestinal and respiratory complications which I already talked about. Starting already with 6 years there is a mortality risk of 3 % which is 20 times higher than in normal populations.

But with today`s treatment options, not everything is bad for PWS children. So I want to end with showing you this girl. She is the baby you saw on the black- and-white pictures in the beginning now at the age of 16. Of course, she is overweight, of course she has her characteristic features and some intellectual deficit, but nevertheless at least at the moment she is a quite happy young girl. Concluding with this, I thank you very much for your attention and give the word to Siggi Kruse as children with Prader-Willi-Syndrome are certainly a group of patients in whom homeopathy can achieve really good effects.