57th ESPE 2018
Meeting ATHENS GREECE
27-29 September 2018

Meet the Expert
HANDOUTS

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Meet the Expert Session

1:1 – 1:2

The role of Radiology in the diagnosis of skeletal dysplasias

Amaka Offiah (Sheffield, UK)
Nadia Amin (Leeds, UK)

- 1:1 Thursday 27 September at 17:15 - 18:15hrs in the Dimitris Mitropoulos Hall

- 1:2 Friday 28 September at 08:30 - 09:30hrs in the MC3 room (MC2 Overflow)

Skeletal Dysplasias

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1. Sheffield Children's NHS Foundation Trust, UK 2. University of Sheffield, UK

The skeletal dysplasias are a heterogenous group of disorders affecting bone development, characterised by abnormal growth, development, differentiation and maintenance of bone and cartilage. Skeletal dysplasias can present at any time from the prenatal period to adult life, and whilst conditions are individually rare the birth incidence collectively is approximately 1:5,000. The approach to the classification of skeletal dysplasias has evolved over time. Initially the approach was based upon clinical and radiological observation, which was subsequently complemented by molecular discoveries that helped to understand them as part of gene disorder groups or pathways. The 2015 nosology and classification of genetic skeletal disorders facilitates the diagnosis of over 400 disorders, categorised into 42 groups of skeletal dysplasias. This includes disorders that lead to short stature such as achondroplasia, disorders with decreased bone density such as osteogenesis imperfecta, disorders with increased bone density like osteopetrosis, and lysosomal storage diseases with skeletal involvement such as many of the mucopolysaccharidoses.

Skeletal disorders may be suspected in the prenatal period during routine ultrasound examination. The fetus may be noted to have growth deficiency, bowing or shortening of long bones, vertebral defects, rib abnormalities, fractures or abnormal calvarial ossification. However, in many of the milder, non-lethal cases patients are not diagnosed prenatally as many of the skeletal dysplasias are the result of abnormalities of the endochondral ossification, a process which is most active during the last trimester of pregnancy.

In childhood the commonest presentation of skeletal dysplasias is with disproportionate short stature, although other clinical manifestations include bone deformities, recurrent fractures or incidental abnormal radiographic findings and extra-skeletal findings such as facial dyspmorphism.
In assessing a patient with a skeletal dysplasia, the initial evaluation requires a thorough history, examination, laboratory investigations and radiographic studies. Key questions in the history include developing an understanding of whether growth restriction is the result of a pre or postnatal growth deficiency, and timing of development of short stature. The family history is valuable in identifying other similarly affected family members and likely inheritance pattern, and questions should be asked for example about short stature, recurrent fractures, limb bowing, retinal detachment, polydactyly and renal disease in the immediate family. A history of joint pain or laxity can also provide valuable clues towards the diagnosis, and a developmental history is imperative.
Examination of the patient should involve attention to body proportions, and auxology should include upper/lower segment ratios, arm span and head circumference. The arm span is obtained by measuring the span of both arms outstretched perpendicular to the axis. The measurement is done between the tip of one middle finger to the tip of the other middle finger. The arm span should be always equal to or greater than the height in children as well as adults and not exceed the height by 10 cm in adults. Children tend to have an arm span that is equal to their height, whereas arm span in adults is usually a few centimeters longer than their height. Rhizomelic shortening is a shortening of the proximal limb segment, e.g. in achondroplasia (not that although children with achondroplasia may appear rhizomelic clinically, radiographs show micromelia) and rhizomelic chondrodysplasia punctata. Mesomelic shortening is a shortening of the middle segment, e.g. Langer mesomelic dysplasia and asphyxiating thoracic dystrophy, and acromelic shortening is shortening of the distal segments (metacarpals, phalanges) e.g. Albright's hereditary osteodystrophy and acrodysostosis.

Micromelia is shortening of extremities involving the entire limb and campomelia is a bowing of limbs. Segment lengths are usually obtained by performing the sitting height in children and adults or by performing crown-to-rump measurements in infants and young children that are not yet walking. The upper segment measurement is divided over the lower segment to obtain the upper to lower segment ratio (US/LS). The ratio is normally higher in young children (e.g. 1.2 to 1.3) but decreases after puberty to 1 or just below 1. A low US/LS ratio indicates either that the extremities are long or that the trunk is short and is useful in determining the nature of the disproportion. A higher number may indicate that the extremities are short. As an example, a child with achondroplasia will show a US/LS ratio ranging from 2 to 1.6 from infancy to adulthood.

Examination should also encompass assessment of dysmorphic features, joint movements, sclera, teeth, finger length, chest deformities, scoliosis, walking pattern and the general systemic examination.

Biochemical and endocrine investigations are likely to be dependent on the clinical picture, with urine glycosaminoglycans (mucopolysaccharides), oligosaccharides, and plasma I-cell screen (elevated plasma lysosomal enzymes such as hexosaminidase) often crucial in patients with dysmorphic features. Specific endocrine conditions are related to specific skeletal dysplasias, such as pseudohypoparathyroidism in maternally inherited Albright's hereditary osteodystrophy.

Radiological assessment is a significant part of making a diagnosis in a child with a suspected skeletal dysplasia. A skeletal survey (including bone age assessment) is the most valuable initial investigation. The skeletal survey allows determination of which areas of bone are affected, and can lead to a general grouping of disorders. The routine dysplasia skeletal survey should include the following images:

Site	Projection(s)
Skull	AP and lateral
Thoracolumbar spine	Lateral
Chest	AP
Pelvis	AP
One upper limb	AP
One lower limb	AP
Left hand and wrist	DP

Limb segment disproportion may be more visible radiologically as clinical assessment may be impeded by skin folds. Additional radiological findings, such as punctate calcifications in rhizomelic chondrodysplasia punctata, dysostosis multiplex in the storage disorders and Wormian bones in osteogenesis imperfecta provide clues to the diagnosis not clinically discernible.

Mutation analysis adds to the diagnostic certainty, may provide additional prognostic information that is of value to the patient and family and (by identifying involved pathways) may be a starting point for the development of novel treatment options.

Meet the Expert Session

2:1 – 2:2

Endocrine complications in Thalassemia

Nicos Skordis (Nicosia, Cyprus)
Andreas Kyriakou (Glasgow, UK)

- 2:1 Thursday 27 September at 17:15 - 18:15hrs in the Nikos Skalkotas Hall

- 2:2 Saturday 29 September at 08:00 - 09:00hrs in the MC3 room (MC2 Overflow)

Endocrine complications in Thalassaemia

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Abstract

Multiple transfusions in patients with Thalassaemia Major (TM) result in iron overload, accumulating in tissues with high levels of transferrin-receptors such as liver, heart and endocrine glands. The nature and frequency of endocrinopathies differ between countries because of differences in treatment regimens followed by centres across the world.

The origin of growth failure is multifactorial: chronic anaemia, hypersplenism, chronic liver disease, skeletal dysplasia, desferrioxamine toxicity, dysfunction of the growth hormone (GH)/IGF-1 axis, hypothyroidism and delayed puberty. Therapeutic response with GH administration in cases with GH deficiency is often less than expected. Iron deposition on gonadotrophic cells of the pituitary leads to disruption of gonadotrophin production and consequently to delayed puberty and hypogonadism, and is the commonest complication. Therapeutic response to sex steroids is excellent in the majority of the cases. Patients with TM usually present after adolescence with impaired glucose tolerance, initially as insulin resistance and subsequently as insulin deficiency. Other contributing factors for the development of Diabetes Mellitus include: liver dysfunction, genetic loading and hormonal treatment. Haemosiderosis of the thyroid and parathyroid glands are the underlying cause of thyroid dysfunction and hypoparathyroidism respectively, which rarely presents after the age of 10 years. Biochemical adrenal insufficiency varies and it is reported to be up to 45%, but clinical adrenal insufficiency is extremely rare. The pathogenesis of bone disease is multifactorial, complicated and still unclear. Patients with TM display an unbalanced bone turnover with an increased resorption phase and decreased formation phase. Endocrine dysregulation continues to be a significant challenge in TM patients due to interrelated factors, affecting their social adjustment and quality of life. Attainment of reproductive capacity is a priority for both young women and men with TM. Early recognition and treatment of endocrinopathies is vital to prevent late complications and increase the chances of parenthood.

Key words: Thalassaemia major, Endocrine complications, Iron overload, Growth Failure, Hypogonadism, Osteoporosis

Introduction

Thalassaemia Major (TM) is characterised by the absence or severe deficiency of b-globin chain synthesis, leading to a profound and symptomatic anaemia that requires regular and life-long transfusion support. TM was known to affect a significant segment of population in Mediterranean countries, Middle and Far East, and North and West Africa. However, the alteration of migration has changed the geographic distribution and has made it a worldwide health problem in the 21st century. Treating patients with TM early with regular blood transfusions during the first decade of life has been shown to improve oxygen carrying capacity, cardiac status, systemic parameters of growth and development and overall well-being.

Our understanding of the mechanisms leading to endocrine disturbances in Thalassaemia has significantly changed during the last three decades culminating in advances in transfusion and chelation treatment as well as the overall care. Multiple transfusions result

in iron overload. Iron accumulates in tissues with high levels of transferrin receptors such as liver, heart and endocrine glands. Improvement in chelation treatment has undoubtedly led to both an increase in life expectancy and decrease in morbidity, however, the clinical picture of TM is still characterised by the consequences of iron overload and chronic hypoxia, of which endocrine abnormalities remain as the most frequent disturbance in TM patients.

The prevalence of endocrine complications varies because of the variability of treatment protocols across the world, the severity of the genetic defects, the levels of haemoglobin and the level of iron load in various patient groups. Another contributing factor is the increased survival to adulthood due to improvement in the medical care of TM patients [1].

Growth failure

The child with TM has a particular growth pattern, which is relatively normal until age 9-10 years; after this age a slowing down of growth velocity and a reduced or absent pubertal growth spurt are observed. The growth plate fusion is usually delayed until the end of the second decade of life [2]. Body disproportion between the upper and lower body segment is observed in approximately 15-40%, mostly attributed to spinal growth impairment that starts during childhood and deteriorates progressively. During puberty, hypogonadism further impairs spinal growth. The pathogenesis of growth failure is multifactorial as shown in figure 1 [3]. Three phases of growth are identified according to age of presentation:

First phase: infancy and childhood <5 years
In the first phase, growth disturbance is mainly due to hypoxia, anaemia, ineffective erythropoiesis and nutritional factors. Chronic anaemia leads to increased erythropoiesis that causes bone marrow expansion. Skeletal changes due to chronic anaemia are already present after 12 months of age. In recent times, chronic hypoxia is no longer a contributing factor in properly treated children and linear growth in this phase is disrupted only in a small percentage of children [1].

Second Phase: childhood 5-10 years
During late childhood, growth retardation is mainly due to iron overload affecting the Growth Hormone (GH)/IGF-1 axis. High serum ferritin levels during the first decade of life predict short adult stature, suggesting that appropriate iron chelation therapy can prevent or limit this complication. However, there remains a high prevalence of short stature in TM children and adolescents treated intensively with desferrioxamine, which may be attributed to toxicity of desferrioxamine itself [4].

Assessment of GH/IGF-1 axis has given contradictory results in children, although the majority of studies report a low GH response to stimulation tests [4]. However, in cases which GH deficiency is established, the response to GH therapy is often less than expected. Treatment with GH for 1 year is effective in increasing growth velocity without causing adverse effects on bone maturation, glucose tolerance, serum lipids and blood pressure. These encouraging results seen during the first year of GH treatment do not persist into the second and the third year, therefore it is not clear whether prolonged therapy with GH improves adult height [5].

Third phase: late childhood and adolescence

During the first decade of life the maintenance of haemoglobin levels above 90g/L together with adequate iron chelation therapy make the children with TM indistinguishable from their peers. However, most children present after the age of 10 years with growth deceleration. Delayed or arrested puberty is an important contributing factor to growth failure in TM adolescents. Hormonal induction of puberty in non-GH deficient boys with TM and delayed puberty does not always result in a significant improvement in growth velocity [6]. Adults with TM who received oral chelation therapy for 6 years or more before attaining their final height had lower liver iron concentration, lower fasting glucose levels, higher IGF-1 levels and a better adult height when compared to those who did not receive oral chelation therapy before attaining their adult height. In addition, the prevalence of endocrinopathies, including hypothyroidism and hypogonadism were significantly lower [7].

Protocol for assessment of growth in TM children

1. Measurement of current height both standing and sitting and plotting on the growth chart. Calculation of the target height based on parental heights. Estimation of growth velocity. Assessment of puberty. Note any physical disproportion. Review caloric intake, emotional and social status.
2. Assessment of bone maturation with bone age.
3. Routine blood tests including liver function tests, ferritin, serum iron, total iron binding capacity and transferrin saturation, anti TGA IgA antibodies and Zinc.
4. Thyroid function tests (Free T4, TSH).
5. IGF-1 and IGFBP-3.
6. Stimulation tests to assess GH secretion. Priming with sex steroids should be considered.
7. IGF-1 generation test in children with low levels of IGF-1 and IGFBP-3 and normal GH secretion to exclude GH resistance.

Pubertal disturbances and Hypogonadism

Hypogonadism remains the most common endocrine complication in TM [1]. Anterior pituitary function (GnRH stimulation test) correlates well with the degree of iron deposition in the pituitary gland, as quantitatively determined by MRI measurements (T2*) [8]. The damage of the hypothalamus and pituitary is progressive, even when intensive chelating therapy is given, and hypogonadism is often unavoidable.

The association of hypogonadotrophic hypogonadism with genotype in TM has already been proven. The contribution of the underlying molecular defect in TM to the development of endocrinopathies in TM and particularly hypogonatotrophic hypogonadism is significant, because the patients with the more severe defects have a greater rate of iron loading through higher red cell consumption and probably a different vulnerability to free radical damage [9].

Adolescent girls with TM often present with primary amenorrhea and boys fail to become well virilised. Most women with TM manifest secondary amenorrhea at some stage in their

life and men develop hypogonadism in their third decade, after having normal androgen production for some years and potentially becoming fathers. Fortunately gonadal iron deposition is a rare condition and most patients should expect to retain gonadal function.

Protocol for investigation for pubertal disturbances
1. Assessment of growth and puberty. The absence of any clinical pubertal signs in a boy (testicular volume >3mL) older than 14 years and in a girl (breast development) older than 13 years requires investigation.
2. Measurements of testosterone in boys and oestradiol in girls.
3. Measurements of basal levels of FSH and LH.
4. GnRH test for evaluation of the pituitary capacity to secrete FSH and LH (this should be done before blood transfusions).
5. Ultrasound of uterus and ovaries in girls.
6. Bone age can be helpful in discussions of treatment options.

The treatment of delayed or arrested puberty and hypogonadotrophic hypogonadism depends on factors such as age, severity of iron overload, damage of the hypothalamo-pituitary-gonadal axis, chronic liver disease, and the presence of psychological problems as a result of hypogonadism. Therefore, each patient has to be assessed individually. The therapeutic approach in delayed puberty should be to mimic biological and biochemical pubertal changes, aiming also to promote linear growth. Induction of puberty, after the age of 13 years in girls and after 14 years in boys, and hormone replacement therapy in those with hypogonadotrophic hypogonadism is recommended.

Fertility

Prolonged life expectancy and the improvement in quality of life are amongst factors that have ascribed to the newfound significance in these patients' desire to optimise their reproductive capacity.

Women with TM have expectations of achieving normal levels of sexual activity and reproductive capacity. Despite hypogonadotrophic hypogonadism and severe iron deposition, ovarian function may be preserved, as women with TM are still able to increase Estradiol levels following gonadotrophin stimulation test. Women with TM who are regularly transfused and are well chelated are able to conceive after a closely monitored treatment [10]. The report of a large number of successful pregnancies so far is highly indicative of the safety of pregnancy in TM women. The desire of the woman with TM to become a mother should be viewed with special caution and sensitivity. Each young woman should be counselled on her suitability to embark on pregnancy with respect to achieving optimum outcomes for both the mother and the foetus. Particular attention should be taken in regards to the maternal cardiac and liver function, as well as the risk of vertical transmission of blood borne viruses.

Males who have normal gonadal function often maintain their spermatogenic ability and therefore, frequently become fathers. On the other side of the spectrum, in cases where impaired spermatogenesis is present, a combination treatment with gonadotrophins has been proven to be beneficial in improving reproductive capacity [10].

Bone Disease

Bone disease may be found in 50-90% of patients with TM worldwide and has become a major cause of skeletal complications. Children and adolescents with TM have lower bone mineral density (BMD) than healthy population and fracture rates are increased and rise with age. Males with TM are more frequently and severely affected from bone disease, in contrast to the well-known predominance of females among patients with osteoporosis in the general population [11].

The pathogenesis of bone disease in TM is multifactorial, complicated and still unclear. Patients with TM display an unbalanced bone turnover with an increased resorption phase and decreased formation phase, resulting in severe bone loss [12]. Additional contributing factors include the presence of endocrinopathies (GH deficiency, hypogonadism), the bone marrow expansion due to ineffective erythropoiesis and the direct iron toxicity on bone that impairs osteoid maturation and inhibits mineralization.

Assessment of bone health in TM patients should begin after the age of 10 years, with annual assessment of serum calcium, phosphate, alkaline phosphatase, vitamin D, parathyroid hormone (PTH) and urinary calcium and phosphate excretion. Assessment of BMD by DXA should be performed every 2 years after the age of 10 years, accompanied by Vertebral Fracture Assessment. Lateral spinal radiographs for vertebral morphometry should be performed at longer intervals, unless there are clinical indications. MRI of the spine may be considered to exclude spinal degenerative skeletal changes.

Prevention is undoubtedly the first step in the management of bone disease in TM. Induction of puberty in a timely fashion and management of hypogonadism are very important steps. Effective iron chelation, improvement of haemoglobin levels, calcium and vitamin D supplementation, physical activity, and smoking cessation are the main preventing measures. The early identification of osteopenia and osteoporosis is of paramount importance, since delayed diagnosis and inadequate treatment may lead to significant osteoporosis, skeletal abnormalities, fractures, spinal deformities, nerve compression and growth failure. The presence of unbalanced bone turnover with an increased resorption phase has justified the use of bisphosphonates, aiming in preventing further loss of BMD. Third generation bisphosphonates are effective in TM patients, decreasing bone resorption, and improving BMD (13).

Hypothyroidism

The pituitary-thyroid axis is less sensitive to iron induced damage than the gonadal and GH axis. Primary hypothyroidism usually appears during the second decade of life, with the subclinical type (normal Free T4, slightly elevated TSH) being the most commonly seen type. The progression of subclinical hypothyroidism to overt disease may take many years and could be prevented with proper chelation therapy. Annual investigation of thyroid function

(TSH, Free T4) should be checked routinely in all patients with TM after the age of 9 years.

Hypoparathyroidism

Hypoparathyroidism is mainly caused by iron deposition in the parathyroid glands and presents after the age of 16 years. The majority of patients present with mild hypocalcaemia and very rarely with tetany and cardiac failure. The diagnosis is based on low serum calcium, elevated phosphate and low PTH levels.

Impaired glucose tolerance and Diabetes Mellitus

The prevalence of impaired glucose tolerance and insulin dependent diabetes mellitus in TM varies from 4% to 20% and increases with age. Diabetes Mellitus is uncommon during the first years of life. Impaired glucose tolerance may start early in the second decade, parallel to puberty. The combined adverse effects of both puberty and TM associated risk factors on insulin action may partly explain the increase of insulin resistance in adolescents. Impaired glucose tolerance is caused mainly by iron overload. Ferritin levels are positively correlated with the fasting and 2-hour blood glucose level in oral glucose tolerance test (OGTT) as well as with the average and the maximum blood glucose level recorded by Continuous Glucose Monitoring System [14].

Impaired glucose tolerance and insulin dependent diabetes mellitus in TM have been predominantly attributed to a combination of reduced insulin secretory capacity and insulin resistance. Early recognition of glucose abnormalities is essential for the prevention, detection and early management of complications of diabetes. OGTT should be performed in all TM patients after the age of ten years or earlier if needed.

Recommendations for glucose homeostasis disturbances include (15):
1. Intensive iron-chelation therapy and prevention and treatment of chronic hepatitis C
2. Management of Diabetes Mellitus should be individualised
3. During initiation of insulin, close blood glucose monitoring (ideally with Continuous Glucose Monitoring System) may help to determine dosage requirements.
4. Patients with TM should strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes
5. There is limited published data on the efficacy and safety of oral antidiabetic agents
6. HbA1c is a poor marker in subjects with diabetes and haemoglobinopathies. Fructosamine determination is useful for monitoring diabetes in these patients.
7. TM women with normal glucose tolerance pre-pregnancy should be advised that they may develop glucose intolerance later in pregnancy, and that repeat OGTT should be performed at both 12–16 and 24–28 weeks gestation with measures at 0, 1 and 2 hours, using the specific gestational diabetes criteria
8. TM women with pre-existing diabetes should have pre-pregnancy counselling and planning to aim for optimal glycemic control before and throughout pregnancy to minimize adverse pregnancy outcomes
9. Patients with TM and diabetes should be seen regularly by a specialised multidisciplinary team with expertise in both diabetes and TM.

Conclusion

Endocrine dysregulation continue to be a significant challenge in TM patients due to interrelated factors, affecting their social adjustment and quality of life. A full evaluation of endocrine complications should be carried out in TM patients with iron overload, particularly after the age of 10 years. Delayed puberty and hypogonadism are the most common endocrinopathies. The aetiology of glucose homeostasis disturbances is multifactorial. Subclinical hypothyroidism requires regular follow-up and optimising chelation therapy. Most patients with hypoparathyroidism show a mild form of the disease. Normalization of total body iron load with very intensive combined chelation therapy reverses cardiac and endocrine complications of TM. Monitoring of growth, pubertal development, reproductive ability, and endocrine function are essential in achieving a good quality of life in TM.

Despite significant advances in transfusion programs and regimens, chelating agents and hormonal replacement, iron overload is still a major consequence. Close follow up, early recognition and proper management is crucial for every patient. During the last 25 years, investigators have made great strides in developing new iron chelators. Many candidate drugs have been screened, but only a few have had the chemical and biological properties suitable for potential clinical application. Some of these are now under intensive investigation. Patients may ultimately benefit from having a choice between several chelators, including orally active drugs. New strategies of chelation, such as combination therapy and organ-targeted chelation may soon have a considerable impact on the therapeutic outcome and quality of life. In the meantime, gene therapy appears defiantly exigent and particularly challenging.

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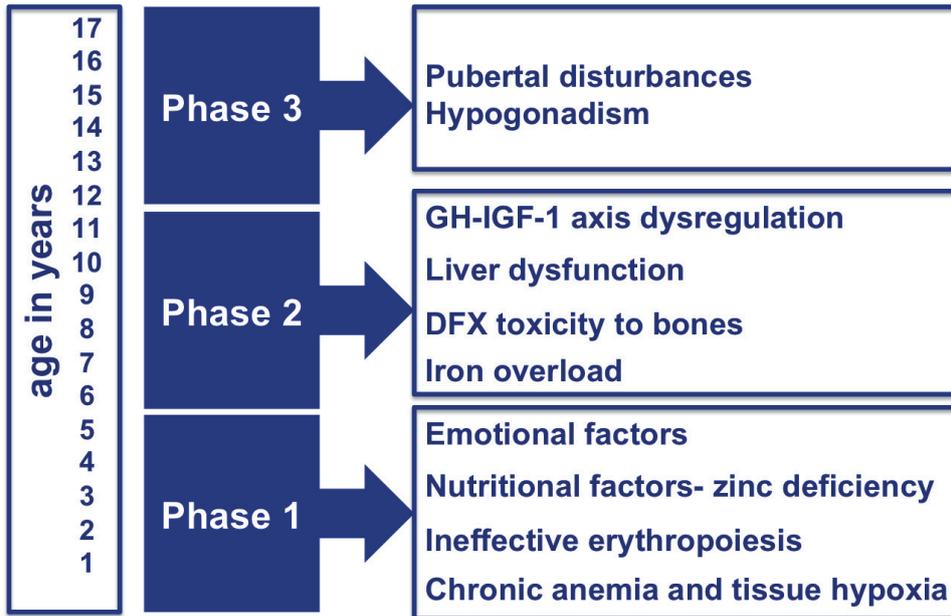
Figure 1. The multifactorial origin of growth failure in Thalassaemia.

Meet the Expert Session

3:1 – 3:2

Neuro endocrine assessment after a childhood intracranial or suprasellar tumour

Helen Spoudeas (London, UK)
Hoong-Wei Gan (London, UK)

- 3:1 Thursday 27 September at 17:15 - 18:15hrs in the Banqueting Hall

- 3:2 Saturday 29 September at 08:00 -09:00hrs in the Banqueting Hall

Childhood brain tumours represent some 25% of childhood cancers. With better histopathological classification, surgical techniques, medical therapies and supportive care, some 80% of children now survive and deserve an independent adult future. However, this success is tempered by a parallel increase in cognitive and endocrine morbidity, and in neurodisability. These receive both less attention and less funding.

A large body of literature from historic cross sectional, institutional case series, on mixed tumour groups receiving whole brain high dose irradiation, has attributed poor cognitive and endocrine outcomes to typical "late", dose-dependent irradiation-induced treatment complications, rather than pre-existing disease (eg.diagnostic delays, hydrocephalus, tumour position, recurrence) or perioperative treatment variables. Hence it is assumed that if radiation can be reduced, better targeted or omitted these can be avoided. The theoretical cognitive and pituitary-sparing advantages afforded by the reduced penumbral scatter of proton beam irradiation has made this the NHS UK standard of care for focal lesions, patients being sent to USA for therapy, without a risk-benefit analysis as compared with photons. However the devastating effects of hypothalamo-pituitary injury from low grade, "benign" tumours remain poorly understood and parallel neuroendocrine rehabilitation pathways - with the data they might generate to challenge these assumptions and improve patient care - are not always timely or routinely prioritised. Furthermore, in multimodal therapy targeting the whole hypothalamopituitary axis, the challenge of separating systemic, chemotherapy-induced, target gland dysfunction from central hypothalamo-pituitary dysfunction, remains .

To address this, we have published an international (SIOP) consensus of endocrine and psychological outcome measures which should be assessed in all randomised neuroncology treatment trials, according to age (under and over 5 years) and tumour position. Using illustrative case studies, and referencing recent international multinational prospective randomised treatment trials of specific tumour types, and our own institutional, 30-year, tumour-specific case series, we will defend the concept that neuroendocrine morbidity is not simply radiation - induced, but rather results from a cumulative, acquired, all-cause brain injury. This importantly includes tumour position (and its proximity or invasion of, vital neurocognitive, ophthalmic, neurometabolic and neuroendocrine pathways) as well as peripheral chemotherapy - induced target gland dysfunction. These vitally impact on the subsequent growth, learning and maturation processes in the developing child. Some of these are life threatening and all are life changing. We believe comprehensive neuroendocrine assessment should be routine from diagnosis, refined according to tumour position (suprasellar versus peripheral cortex / brain stem), and treatment (+/- chemotherapy, skeletal radiation), and continuous across maturational transitions (infancy, childhood, adolescence, adulthood). In this way it can inform timely endocrine replacement, targeted remediation and improve function and health related quality of life and urgently needs implementing into clinical research and acute oncology treatment pathways.

Meet the Expert Session

4:1 – 4:2

The use of modern technologies to optimise diabetes care

Olga Kordonouri (Hannover, Germany)

- 4:1 Thursday 27 September at 17:15 - 18:15hrs in the Alexandra Trianti Hall

- 4:2 Saturday 29 September at 14:00 - 15:00hrs in the Alexandra Trianti Hall

The Use of Modern Technologies to Optimize Diabetes Care

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The gold standard for the treatment of Type 1 diabetes in children and adolescents is the intensified insulin therapy using either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) pump according to the basal-bolus-principle. Blood glucose measurement is the mainstay of diabetes management, guiding insulin dosing decisions and monitoring glycemic control.

New technological advances including subcutaneous continuous glucose monitoring (CGM), either from real-time (rtCGM) or intermittent scan use (iscCGM), are of particular importance for children and adolescents due to the age-related metabolic fluctuations. These systems are both for physician's orientation as well as for patient use (*Figure 1*). They provide more information about intra- and interday glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia, which have been linked to both microvascular and macrovascular complications. In Germany and in other countries we are observing a huge increase in the use of insulin pump and CGM systems (*Figure 2*).

On the basis of CGM data a new parameter "Time in range (TIR)" has been developed. TIR generally refers to the time spent in an individual's target glucose range (usually 70–180 mg/dL [3.9–10 mmol/L]. TIR measurements add valuable information to assess the level of current glycemic control. Both rtCGM and iCGM facilitate monitoring of time spent in- and outside the target glucose range, new parameters that can be used by both, patients and health care providers, in addition to glycated hemoglobin (HbA1c), which has been the traditional method for assessing glycemic control so far. Standardizing glucose reporting and analysis is vital to optimizing clinical decision-making in diabetes care. Therefore, standardized tools such as the Ambulatory Glucose Profile (AGP), Pattern Snapshot (Medtronic), Clarity (Dexcom), and others from various device makers and data management companies are now available. Minimum requirements for CGM performances and key metrics for CGM data analysis and reporting have been defined by the Expert Panel (*Figure 3*) [3].

Furthermore, the combination of CSII and rtCGM in form of a sensor-augmented pump (SaP) treatment allows semi-automated insulin dosing with the aim of reduction of hypo- and hyperglycemia in patients with Type 1 diabetes.

Current studies show that the implementation of modern technologies into diabetes treatment can help the optimization of metabolic control and also lead to improved quality of life both in patients with type 1 diabetes and in their families.

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Figure 1: Overview of current systems for continuous glucose monitoring and their characteristics. rtCGM: real-time continuous glucose monitoring; iscCGM: intermittent scan continuous glucose monitoring

Increasing Use of *rt- / isc-CGM* in Children/Adolescents in Germany
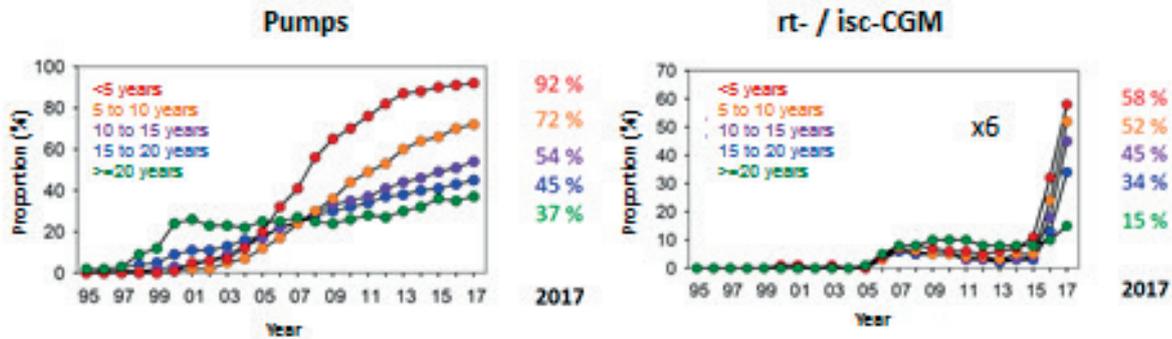

Figure 2: Increasing use of insulin pump and CGM systems in children, adolescents and young adults with type 1 diabetes in Germany.

Parameters of standardized CGM-Reports

Figure 3: List of parameters for standardized data analysis and reporting as required by the International Consensus on Use of Continuous Glucose Monitoring [3].

Meet the Expert Session

5:1 – 5:2

Reproductive function in CAH

Hedi Claahsen-van-der Grinten
(Nijmegen, The Netherlands)
Karijn Pijnenburg
(Nijmegen, The Netherlands)

- 5:1 Friday 28 September at 08:30 -09:30hrs in the Banqueting Hall

- 5:2 Saturday 29 September at 08:00 - 09:00hrs in the Alexandra Trianti Hall

Gonadal dysfunction in congenital adrenal hyperplasia

Hedi L. Claahsen – van der Grinten, MD, PhD, paediatric endocrinologist
Karijn J. Pijnenburg – Kleizen, MD, paediatric endocrinologist in training
Amalia Children's Hospital, Radboud University Nijmegen Medical Center, The Netherlands

Introduction

Impairment of gonadal function is a serious complication in patients with congenital adrenal hyperplasia (CAH). It can result in menstrual disturbances in females, and hypogonadism and infertility in both male and female patients. Infertility can also result from psychological and/or surgical long-term complications (Table 1). Since nowadays nearly all CAH patients reach adulthood with a good quality of life, knowledge about this long term complication and the underlying mechanisms is important for all pediatric endocrinologists who take care of CAH patients. In this mini-review we focus on gonadal dysfunction that can already occur during puberty and young adulthood. For a complete overview of all causes of infertility in CAH patients we refer to more comprehensive review papers. [1, 2]

Gonadal dysfunction in male CAH patients

In male CAH patients, reproductive function can be impaired due to primary gonadal failure, mainly caused by the presence of testicular tumours. [3] Another important factor contributing to testicular dysfunction is suppression of the hypothalamic-pituitary-gonadal axis due to high circulating levels of androgens, resulting in secondary gonadal failure (Figure 1).

Testicular adrenal rest tumours (TART)

Typical testicular tumours in male patients with CAH were already described in 1940. Since then, several case reports and larger studies were published. [4, 5] Histologically, these benign tumours resemble adrenocortical cells and they were originally thought to arise from aberrant adrenal cells in the testes that are stimulated by elevated ACTH. Therefore, they were named testicular adrenal rest tumours (TART). TART are often present bilaterally (> 80% of the cases) and have a typical central location within the rete testes. The reported prevalence varies between 0-94% and depends mainly on the method of detection, age of the patient and severity of CAH. TART lesions below 2 cm are generally not detectable by palpation due to the central location within the testes. Therefore, we recommend using imaging techniques such as ultrasound or MRI. With ultrasound, small lesions of several mm can be detected as hypoechogenic well-delineated masses, often multi-lobular, located around the mediastinum testes. In most papers using ultrasound, a prevalence of about 30% - 50% is reported in adult CAH patients. However, TART can already be detected during childhood with a clear increase in prevalence during puberty and adulthood. [6] TART is mainly present in males with classic forms of CAH (salt wasting, simple virilising). Only one paper describes two patients with the non classic form of CAH with TART.
It is thought that elevated ACTH levels play an important role in the pathogenesis of TART. Several case reports described shrinkage of the tumour after intensifying glucocorticoid therapy and consequently suppression of ACTH. As ACTH and Angiotensin (AII) receptors as well as adrenal specific enzymes and hormones were found in TART tissue, an adrenal origin of TART was deemed very likely. However, several unsolved questions remain. TART is also found in well controlled patients and a clear correlation between hormonal control and prevalence or tumour size has not been found. [7] More recently, Leydig cell specific features of TART tissue were described suggesting that TART consists of a more totipotent celltype. [8] Thus, the etiology of TART has still not been completely clarified.

Due to the central location in the testes TART can lead to mechanical obstruction of the seminiferous tubules with consequently obstructive azoospermia. This longstanding obstruction can result in irreversible damage to the surrounding testicular tissue. In addition, paracrine effects of the steroids produced by TART on the surrounding tissue have been described, that may be damaging to Sertoli cells or germ cells.

As TART is most often described in patients with poor hormonal control, intensifying glucocorticoid treatment is the first choice of treatment. This will lead to a decrease of ACTH levels and in some patients this results in reduction of tumour size and improving testicular function. However, medical treatment is not always successful and with higher dosages of glucocorticoids the risk of serious side effects such as hypertension and weight gain may increase. Testis sparing surgery as a treatment option for TART has been described in several papers. In our clinic we treated 8 adult male patients with longstanding TART with testis sparing surgery. [9] However, we did not find a significant improvement of gonadal function after surgery, suggesting there was already irreversible damage to the testicular tissue. This was confirmed by testis biopsies. Therefore, patients should be informed about the consequences of TART, and cryopreservation of semen should be offered as soon as possible. As TART can already occur in childhood with a clear increase in prevalence during puberty we recommend yearly ultrasound of the testes in patients with classic CAH especially in poor hormonal control.

Secondary gonadal failure in male CAH patients

Especially poorly controlled CAH patients are at risk of developing secondary gonadal failure. [4] High concentrations of adrenal androgens (androstenedione) are aromatised to estrone which will suppress the hypothalamic-pituitary-gonadal axis, leading to hypogonadotropic hypogonadism and small testes. Some authors suggest that steroids produced by testicular adrenal rest tumours may also contribute to the suppression of gonadotropines. However, clinically these two conditions cannot be distinguished.

In contrast to other forms of secondary hypogonadism, most patients do not report any complaints from testosterone deficiency as male CAH patients with poor hormonal control usually have sufficient testosterone from adrenal origin. A typical biochemical profile in this situation is suppressed or normal gonadotropines with a normal testosterone level, but low inhibin B levels. [10] Therefore, even in patients with apparently normal gonadotropin and testosterone levels, gonadal function can be severely impaired. Inihibin B seems to be a better marker for Sertoli cell function and should be checked regularly. To distinguish testosterone from adrenal and testicular origin, it has been suggested to use the serum androstenedione to testosterone ratio in male CAH patients, as androstenedione is elevated when the androgens are predominantly of adrenal origin. [11] One has to be aware that serum total testosterone can be decreased due to low serum SHBG concentrations, for example in obese patients, or elevated in some conditions such as hepatitis or hyperthyroidism. Therefore, free testosterone should be measured or calculated from total testosterone, SHBG and albumin concentrations.

In the absence of TART, most reports show reversible hypogonadism and improved fertility after initiating or increasing glucocorticoid therapy.

Gonadal dysfunction in female CAH patients

Gonadal dysfunction in female adolescent and young adult CAH patients can result in abnormal pubertal development, amenorrhoea and irregular menses. Timing of puberty and age at menarche is usually not significantly different in CAH and non-CAH females. However, elevated adrenal steroids can lead to menstrual irregularity. Therefore, a regular menstrual cycle is a good marker for adequate hormonal control.

In general, in female CAH patients gonadal function can be impaired due to several factors: overproduction of adrenal androgens, elevated adrenal steroid precursors (17-hydroxyprogesterone and progesterone), polycystic ovarian syndrome (PCOS) and ovarian adrenal rest tumours. Furthermore, as described previously in CAH males, hypogonadotropic hypogonadism can interfere with gonadal function (see section secondary gonadal failure in male CAH patients). For a more detailed description of fertility in female CAH patients we refer to the literature. [12]

Adrenal overproduction of androgens in female CAH patients

In case of poor hormonal control, elevated adrenal androgens can affect ovarian function, resulting in menstrual disturbances. [1] Androgen excess can inhibit folliculogenesis and may have a negative effect on ovulation. Suppression of adrenal androgen secretion by increasing the glucocorticoid dose can restore ovulation and normalize the menstrual cycle.

Adrenal overproduction of progestins

In some patients, adequate suppression of androgen levels seems to be insufficient to correct menstrual abnormalities. It has been described that increased levels of adrenal steroid precursors (progesterone and 17-hydroxyprogesterone) may interfere with the normal menstrual cycle. The underlying mechanism is that elevated adrenal progestin levels may cause persistent inhibition of follicular growth, inhibition of endometrial proliferation and failure of endometrial breakdown, resulting in menstrual disorders, comparable to the effect of progestin-only contraceptives. In addition, elevated progesterone levels from adrenal origin can cause impermeability of the cervical mucus. [12]
Thus, adequate suppression of adrenal progestins as well as androgens is needed for menarche and for a regular menstrual cycle. However, lowering of 17-hydroxyprogesterone and progesterone levels can usually only be achieved with supraphysiological dosages of glucocorticoids. Finding the balance between over- and undertreatment is an important task of the paediatric endocrinologist.

Polycystic ovarian syndrome (PCOS)

Androgen excess and menstrual disturbances are not only present in CAH patients, but are also important characteristics of PCOS. The pathogenesis of PCOS is still uncertain but there is evidence that the elevated androgens result from ovarian androgen overproduction. Therefore, untreated or poorly treated female CAH patients can have a similar clinical presentation to PCOS patients, including sonographic evidence of ovarian cysts that can be stimulated by adrenal hyperandrogenism. In PCOS as well as in CAH, significantly elevated levels of androgens, 17-hydroxyprogestrone and insulin insensitivity have been described. Several studies report a higher prevalence of nonclassic (NC) CAH in female patients with the clinical picture of hyperandrogenism and PCOS. [13] The distinction between these two conditions can be difficult. The distinction can be made using a synacthentest with measurement of 17-hydroxyprogestrone, and molecular analysis of the *CYP21A2* gene.
In general, the prevalence of PCOS in CAH is comparable to the general population. Stikkelbroeck *et al.* investigated the prevalence of PCOS in 13 female patients with CAH. Polycystic ovaries were found in two patients (15.4%). [12] Therefore, PCOS is not a common cause of menstrual disturbances in CAH females.

Ovarian adrenal rest tumours

In contrast to the high prevalence of TART in male CAH patients, ovarian adrenal rest tumours (OART) seem to be very rare. So far only a few case reports have been published. It can be suggested that the low prevalence can be explained by the difficulty to detect these tumours as the ovaries are not as accessible to imaging as the testes. In a small study of 13 adult female patients from our own group no ovarian adrenal rests were detected by ultrasound or MRI. 18 F-FDG PET/CT was used to study ectopic ovarian rests in CAH female in several studies. Selective venous sampling and complete pelvic venous sampling to localize virilizing ovarian tumours was also described in several case reports. When routine imaging techniques fail to detect these lesions, pelvic venous sampling might effectively localize the tumours. This may be especially important when female CAH patients suffer from an unexplained increase of adrenal androgens. One case report described a young adult female CAH patient who underwent bilateral adrenalectomy because of poorly controlled CAH. Several years

after surgery, she developed secondary amenorrhea and hair loss as a result of adrenal androgen excess caused by ovarian adrenal rests only detectable by pelvic venous sampling. [14] This case clearly illustrates that a chronically elevated ACTH may induce proliferation of adrenal rest cells in females within the ovaries, leading to androgen excess and thereby undoing the beneficial effect of adrenalectomy.

Practice recommendations

Optimal hormonal control is a key factor for adequate gonadal function in male and female CAH patients, already during adolescence and young adulthood.

In all adolescent CAH patients, evaluation of hormonal control by regular measurements of adrenal steroids throughout the day should be performed.

In females: Asses the regularity of the menstrual cycle during each visit. When amenorrhea or irregular menstruation is present, measurement of androstenedione, 17OH progesterone and progesterone is recommended to rule out hormonal causes of gonadal dysfunction. Consider intensifying glucocorticoid treatment even when androstenedione levels are suppressed, with careful monitoring of 17 OH progesterone and side effects from supraphysiological dosages of glucocorticoids. Routine imaging to detect ovarian adrenal rests and polycystic ovaries is not recommended.

In males: Yearly evaluation for TART using ultrasonography is recommended from the start of puberty, but only in classic forms of CAH. We recommend yearly evaluation of gonadal function by measuring LH, FSH, (free) testosterone, SHBG and inhibin B. Normal levels of gonadotropines and testosterone do not rule out gonadal dysfunction especially in patients with small testis volumes. Consider using the androstenedione to testosterone ratio to differentiate between an adrenal and a testicular origin of the androgens. When TART is present, the patient should be referred to an urologist for evaluation and cryopreservation of semen as soon as possible.

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Males	
Gonadal dysfunction	Primary gonadal failure: testicular adrenal rest tumours (TART)
	Secondary gonadal failure: hypogonadotropic hypogonadism due to poor hormonal control
Psychosexual factors	
Females	
Gonadal dysfunction	Overproduction of adrenal androgens
	Overproduction of adrenal progestins
	Polycystic ovarian syndrome (PCOS)
	Ovarian adrenal rest tumours
Anatomical/surgical complications	
Psychosexual factors	

Table 1. Causes of infertility related to congenital adrenal hyperplasia
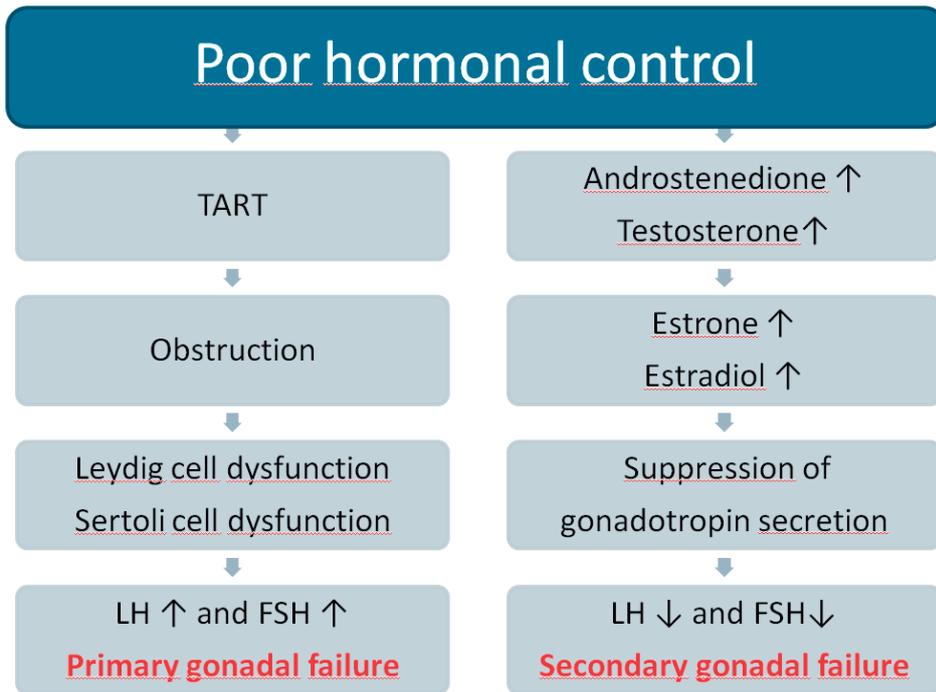
Figure 1. Gonadal dysfunction in male patients with congenital adrenal hyperplasia in relation to poor hormonal control

57th ESPE 2018
Meeting ATHENS GREECE
27-29 September 2018

Meet the Expert Session

6:1 – 6:2

Management of Hypo & Hypercalcaemia

Nick Shaw (Birmingham, UK)
Ruchi Nadar   (Birmingham, UK)

- 6:1 Friday 28 September 2018 at 008:30 -09:30hrs in the Alexandra Trianti Hall

- 6:2 Saturday 29 September 2018 at 08:00 - 09:00hrs in the Dimitris Mitropoulos Hall

Management of Hypo and Hypercalcaemia

Nick Shaw and Ruchi Nadar

Department of Endocrinology & Diabetes, Birmingham Children's Hospital, UK

This review will provide a brief overview of this topic which embraces a range of disorders seen in children and adolescents. For a more detailed description of the topic readers are recommended to access these reviews (1- 3).

Physiology

There are three key components in the regulation of plasma calcium disturbances of which may lead to a presentation with hypo or hypercalcaemia. These are the calcium sensing receptor, parathyroid hormone (PTH) and the active metabolite of vitamin D, 1,25 dihydroxyvitamin D_3 $(1,25(OH)_2D_3)$. A fall in plasma calcium leads to a cascade of events terminating in the action of PTH on the target organs leading to a restoration of plasma calcium to normal. The first event is stimulation of the calcium sensing receptor (CaSR) which is present in many tissues but particularly the parathyroid glands and the renal tubules. This leads to the rapid synthesis and release of PTH from the chief cells of the parathyroid glands. This interacts with the key target organs of bone and the kidney, in the former by stimulating osteoclast mediated bone resorption and in the latter by increasing renal tubular calcium reabsorption. An indirect action of the raised PTH is to stimulate the one-alpha hydroxylase enzyme in the kidney to synthesise additional $1,25(OH)_2D_3$ leading to increased intestinal absorption of calcium. Thus by these important physiological actions plasma calcium returns to normal.

 When feedback mechanisms are intact, an elevated calcium level will be sensed by the CaSR leading to suppression of PTH release. Low PTH will decrease the synthesis of $1,25,(OH)_2D_3$, in addition to decreasing calcium influx from the kidney and intestine, normalizing calcium levels. This feedback decrease in PTH secretion is lost in PTH dependent hypercalcemia.

Investigations

It is important to initiate appropriate investigations at the time of presentation and prior to the initiation of any treatment which may confuse the clinical picture. Measurement of plasma phosphate, alkaline phosphatase and magnesium are important. Assessment of renal tubular handing of calcium by performing a urine calcium to creatinine ratio on a single sample is important as is a plasma creatinine to ensure normal renal function. Measurement of 25 hydroxyvitamin D and obtaining a stored sample for $1,25(OH)_2D_3$ are important in both conditions. The key investigation is the measurement of serum PTH at the time of hypo or hypercalcaemia, the response of which provides valuable information as to the likely aetiology and the direction of further investigations. Additional relevant

investigations may include checking the plasma calcium of the parents, a renal ultrasound scan and plain X-rays of wrist and knee. Many of the disorders have a genetic basis so obtaining a DNA sample for subsequent analysis is relevant.

Hypocalcaemia

Children presenting with hypocalcaemia often have symptoms that reflect the importance of plasma calcium in neuromuscular function. Common symptoms include convulsions which can be focal or generalised and muscle cramps such as jaw-locking or tetany. Parasthesiae, a tingling sensation, often around the mouth or in fingers and toes is another common symptom. Signs of chronic hypocalcaemia include basal ganglia calcification, cataracts and papilloedema.

It is possible to categorise the cause of hypocalcaemia into three broad groups depending on the PTH response at the time of hypocalcaemia (see Figure 1). A low PTH level which would be an inappropriate physiological response is seen either in Hypoparathyroidism or Hypomagnesaemia. An inappropriately normal PTH often suggests the presence of an abnormality of the calcium sensing receptor. A high PTH is usually seen in disorders of PTH resistance (inactivating PTH/PTHrP signalling disorder) or a Vitamin D disorder either deficiency or a defect in its metabolism. Chronic renal failure or Infantile Osteopetrosis may also present with this biochemical picture. The following sections will review key features of these conditions:

Hypocalcaemia with a low PTH

a) Hypoparathyroidism

This may be congenital or acquired, the former usually presenting as hypocalcaemic convulsions in the first few weeks of life. Congenital hypoparathyroidism may be an isolated entity or in association with other developmental defects. The isolated forms can be inherited as autosomal dominant or recessive or X-linked recessive. The most common cause is due to mutations in the glial cell missing 2 gene (GCM2) which codes for a transcription factor responsible for parathyroid gland development – this can be dominantly or recessively inherited.

The most well-known syndrome associated with congenital hypoparathyroidism is Di George Syndrome in which hypoplasia of the parathyroid glands occurs during development. In this condition hypocalcaemia is often identified in infancy when the child presents with the known associated cardiac defects. This may require treatment with calcium supplements and/or a vitamin D analogue but will often resolve in early childhood to recur during puberty

or adulthood. Other important conditions are the Hypoparathyroidism, deafness and renal anomalies (HDR) syndrome due to an autosomal dominantly inherited GATA3 mutation on Chromosome 10 and the Hypoparathyroidism, Retardation and Dysmorphism (HRD) syndrome inherited in an autosomal recessive manner. This condition also referred to as Sanjad-Sakati syndrome is common in the Middle East and is due to a mutation in the tubulin-specific chaperone E (TBCE) gene on Chromosome 1.

Acquired hypoparathyroidism may be a consequence of surgery to the neck eg for thyroid disease or as a consequence of iron deposition in the parathyroid glands from repeated blood transfusions in children with Thalassaemia major or rarely as a complication of Wilson's disease. The most important cause of acquired hypoparathyroidism is the autoimmune polyendocrinopathy syndrome APECED due to mutations in the autoimmune regulator gene inherited in an autosomal recessive manner. This condition often presents with hypoparathyroidism as the first endocrine manifestation with the subsequent potential development of adrenal insufficiency, hypogonadism, thyroid disease and diabetes mellitus over several decades. Non endocrine manifestations include malabsorption, chronic active hepatitis and hyposplenism. It is important to consider this condition in any child presenting with hypoparathyoidism in early to mid childhood and once a gene defect is identified to ensure that any siblings are investigated. Any child with this condition should undergo annual screening for adrenal insufficiency as a potentially lethal complication.

b) Hypomagnesaemia

Serum magnesium levels are normally maintained between 0.7 to 1.2 mmoL/L. Magnesium metabolism is linked with calcium metabolism, at the level of the CaSR. Severe hypomagnesaemia impairs PTH secretion in response to hypocalcaemia by raising the threshold for PTH secretion. Genetic forms of hypomagnesaemia (Normocalciuric renal hypomagnesemia) are associated with mutations in genes encoding TRPM6 and EGF which are involved in active reabsorption of magnesium in the distal convoluted tubules. Hypomagnesemia may be seen with the use of certain drugs (diuretics, gentamicin, mercury-containing laxatives or cisplatin), in diabetic ketoacidosis, post renal transplant and urinary tract obstruction. When low plasma magnesium levels are associated with hypocalcaemia, correction of magnesium levels is essential to normalize plasma calcium values.

Hypocalcaemia with a normal PTH

a) Autosomal dominant hypocalcaemia

This combination often suggests an abnormality of the calcium sensing receptor (CaSR) where gain of function mutations cause the condition known as autosomal dominant hypocalcaemia(ADH). The most common form, ADH Type 1 is due to a mutation in the CaSR gene whereas a second form ADH Type 2 is due to a mutation in the GNA11 gene. In this condition there is an altered setpoint in the parathyroid glands and kidneys such that a lower plasma calcium is required to trigger PTH release. Such individuals have a plasma calcium below the normal range often 1.8 to 2.0 mmol/l and increased renal calcium excretion. In at least 40% of affected individuals the PTH is within the normal range whereas the rest will have a low PTH. Approximately 50% of individuals with ADH are asymptomatic whereas the other 50% especially children will be symptomatic during febrile episodes or in the neonatal period. Treatment with a vitamin D analogue and/or calcium supplements should be reserved for symptomatic individuals due to the high risk of hypercalciuria and nephrocalcinosis. An alternative treatment option is the use of synthetic PTH by subcutaneous injection or infusion with a pump.

Hypocalcaemia with a high PTH

a) Pseudohypoparathyroidism

This term covers a number of related disorders in which resistance to PTH is the predominant feature. Those that present with hypocalcaemia resemble hypoparathyroidism with an elevated plasma phosphate but instead of a low PTH have a high PTH. Most of the disorders are due to a genetic or epigenetic defect in the GNAS gene on Chromosome 20 and are an example of imprinting ie repression of gene expression from one parental allele. There are several types with distinctive features. The most well known type is Pseudohypoparathyroidism Type 1a in which affected individuals have features of Albright's Hereditary Osteodystrophy (AHO) which include a round face, truncal obesity, short stature post puberty, shortening of the 4th and 5th metacarpals, heterotopic ossification and/or mental retardation. Affected individuals will often have other evidence of hormone resistance such as hypothyroidism and hypogonadism and may also have evidence of growth hormone deficiency. Although this is a congenital disorder hypocalcaemia does not usually present until mid-childhood which is due to the fact that paternal silencing of G_s alpha expression in the proximal renal tubule occurs postnatally.

Pseudohypoparathyroidism Type 1b does not have AHO features but can also have additional hormone resistance particularly hypothyroidism. PTH resistance develops over time and affected individuals often do not present with hypocalcaemia until their teenage

years. It is now recognised that there is considerable overlap in the different types of pseudohypoparathyroidism which has led to a different classification(4).

b) Disorder of Vitamin D

Although vitamin D deficiency will most often present with rickets in children it can present with symptomatic hypocalcaemia particularly during the rapid growth periods of infancy and puberty. This will be usually as hypocalcaemic convulsions or episodes of tetany. Another important presentation in infancy is with cardiomyopathy which can be life threatening. A phenomenon that can be seen in these age groups is the presence of a raised plasma phosphate despite a high PTH level which occasionally can cause confusion with pseudohypoparathyroidism. This PTH resistance in the renal tubules appears to be due to associated dietary calcium deficiency which well correct when adequate calcium intake is supplied.

Any of the calciopenic forms of rickets due to defects in vitamin D metabolism or action may present with hypocalcaemia. Chronic renal or liver failure can also present with hypocalcaemia although rickets is a more common presenting feature. In the former it is due to inadequate synthesis of $1,25(OH)_2D_3$ and the failure to excrete phosphate whilst in liver failure it is predominantly due to malabsorption of calcium and vitamin D.

c) Osteopetrosis

Infantile osteopetrosis may present in the neonatal period with hypocalcaemia due to a failure of osteoclast action to allow bone resorption. Affected babies will have a high PTH and the failure to respond to conventional doses of a vitamin D analogue and calcium supplements should prompt an X-ray of a wrist or knee which will demonstrate the characteristic dense bones.

Treatment of Hypocalcaemia

This is dependent on two factors 1) whether there are severe symptoms such as convulsions and 2) the underlying cause.

Urgent correction: Intravenous bolus of 10% Calcium Gluconate in a dose of 1 to 2 mls/kg over 5 to 10 minutes (with a maximum of 20 mL) followed by a continuous infusion of 1.0 mmol/kg (maximum 8.8 mmol) over 24 hours. It is important to try and discontinue an intravenous infusion once the severe symptoms have settled in favour of oral calcium

supplements due to the risk of extravasation of calcium causing damage to skin and subcutaneous tissues.

Non urgent correction: Oral calcium supplements are given in a dose ranging from 0.2 mmol/kg to a maximum of 10 mmol/kg four times daily.

Hypomagnesaemia can be treated with intramuscular or intravenous infusion of 50% magnesium sulphate 0.1-0.2mL/kg (50-100 mg/kg). This should be followed by oral magnesium at the dose of 0.2 to 0.4 mmol/kg/day. Primary hypomagnesemia requires long term oral supplementation with 0.7 to 3.5 mmol/kg/day.

Hypoparathyroidism and Pseudohypoparathyroidism:

A vitamin D analogue such as 1 alpha hydroxyvitamin D (Alpha calcidol) or $1,25(OH)_2D_3$ (Calcitriol) in a dose of 25 -50 ng/kg/day to increase intestinal calcium absorption. Calcium supplements are usually required initially but can often be discontinued when the plasma calcium is normal if there is an adequate dietary calcium intake. The aim should be to maintain the plasma calcium at the lower end of the normal range (2.0 to 2.2 mmol/l) as renal calcium reabsorption in the kidneys is low due to the lack of PTH activity with the risk of hypercalciuria. Monitoring should therefore include periodic assessment of the urine calcium/creatinine ratio and renal ultrasounds to detect nephrocalcinosis.

An alternative option if there are problems in managing hypoparathyroidism is the use of synthetic PTH either as twice daily injections or as a continuous subcutaneous infusion which has been shown to be successful.

Vitamin D disorders

Vitamin D deficiency should be treated with ergocalciferol (D_2) or cholecalciferol (D_3) in doses ranging from 3,000 to 10,000 units daily for 8 to 12 weeks or as a single large bolus dose of 150,000 to 300,000 units. Calcium supplements should also be given initially.

One alpha hydroxylase deficiency (Vitamin D dependant rickets Type 1) requires alphacalcidol or calcitriol in conjunction with calcium supplements. Hereditary $1,25(OH)_2D_3$ resistant rickets (Vitamin D dependant rickets Type II) may respond to alphacalcidol or calcitriol in the milder forms but will often require intravenous calcium infusions via a central line to heal the rickets and correct thehypocalcaemia
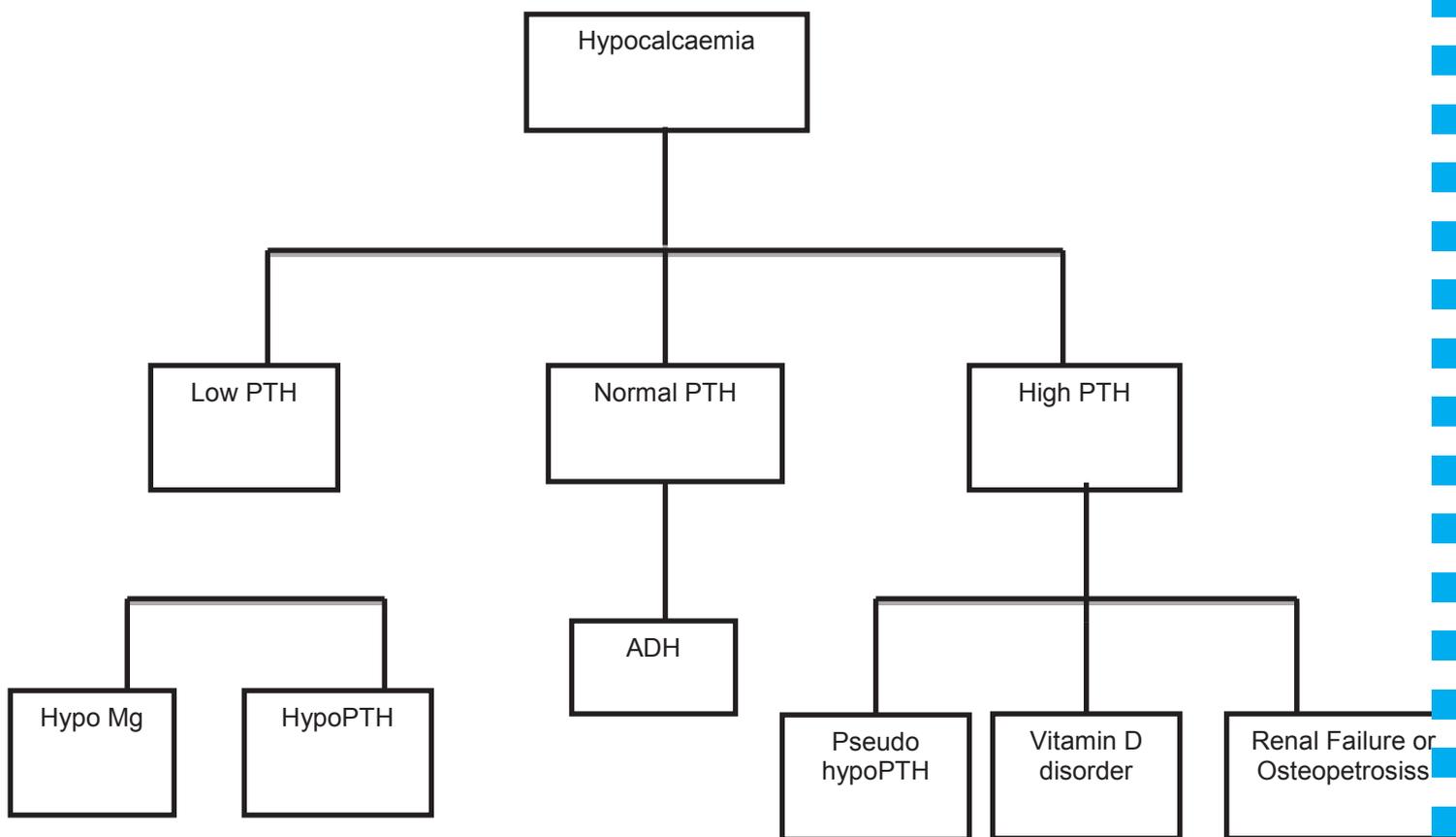
Figure1: Flowchart for Hypocalcaemia

Hypercalcaemia

Hypercalcaemia can be particularly challenging to the clinician due to its varying grades of severity, wide differential diagnosis and rare occurrence. Children with hypercalcaemia can be completely asymptomatic. Symptoms, when present, have an insidious onset over few weeks. Some typical features include nausea, loss of appetite, abdominal pain and constipation. Neuromuscular features such as irritability, lethargy and muscular hypotonia may be seen. Polyuria and dehydration are common in symptomatic cases. Chronically elevated calcium levels can cause pancreatic calcification and renal calculi.

Disorders causing hypercalcaemia can be classified as PTH dependent and PTH independent causes (See Table) depending on whether the PTH level is elevated or suppressed at the time of presentation.

PTH DEPENDENT HYPERCALCAEMIA

a) PHPT (Primary hyperparathyroidism): This is rare in children and accounts for 1% of cases of childhood hypercalcaemia, with an incidence of 2-5 per 100,000. It mainly presents in adolescents with very few cases presenting in the neonatal period. The key biochemical features are elevated or inappropriately normal levels of PTH in the setting of a high normal or elevated calcium concentration. 5-15% of cases are with genetic syndromes. Examples of genes causing this abnormality are PRAD1 (parathyroid adenoma), or those that predispose to multiple endocrine neoplasia; MEN I, IIa and IV.

PHPT is often more aggressive when presenting in children, with bone pains and muscle aches being common. Diagnosis can be delayed due to non-specific symptoms and end organ damage can be present at presentation. Renal complications such as nephrolithiasis, nephrocalcinosis, and renal failure occur frequently in this condition. Calcium deposition may be seen in the eye. X-rays shows features of sub-periosteal bone resorption, brown tumours and pathological fractures. The milder forms are clinically difficult to differentiate from cases with CaSR mutations.

b) Hyperparathyroidism-Jaw Tumour Syndrome**:** Here parathyroid adenomas are associated with tumours of the mandible and maxilla, however parathyroid involvement occurs only during adulthood or adolescence.

c) Tertiary Hyperparathyroidism**:** This condition, seen most commonly in children with chronic renal failure is a result of prolonged, persistent hypocalcemic stimulation of the parathyroid glands, causing the glands to become autonomous. It can sometimes be due to severe prolonged Vitamin D deficiency.

d) Neonatal severe hyperparathyroidism (NSHPT) presents within the first few weeks of life with severe hypercalcemia. It is an autosomal recessive condition and occurs due to homozygous inactivating mutations in the CaSR gene. The majority of affected infants require parathyroid surgery after prior hyperhydration and bisphosphonates.

PTH INDEPENDENT CAUSES OF HYPERCALCAEMIA:

a)Familial hypocalciuric hypercalcaemia results from heterozygous inactivating mutations of the CaSR resulting in an elevation of the normal set point for maintaining plasma calcium levels. The PTH levels are 'unsuppressed' for the level of hypercalcemia and serum PTH may be normal or mildly elevated. A reduced urinary calcium excretion is a distinctive feature. Children with this disorder are usually asymptomatic and identified coincidentally. It is an autosomal dominant condition and therefore if suspected important to check plasma

calcium in both parents. It is due to loss of function mutations in one of three genes (FHH Types 1, 2 &3) with the commonest being FHH Type 1 due to a mutation in the CaSR gene. As it is asymptomatic and does not usually cause long term problems it can be followed up without any intervention (5).

b) Childhood malignancy: Unlike in adults with malignancies, where hypercalcaemia is more common and predicts a poor outcome, in children hypercalcaemia is rare. The various mechanisms are: local osteolytic hypercalcaemia (acute leukaemia); humoral hypercalcaemia of malignancy due to secretion of PTHrP (lymphoma, medulloblastoma) and secretion of $1,25(OH)_2D_3$ (lymphoma/ovarian dysgerminoma).

c) Granulomatous disorders

In these disorders hypercalcaemia is due to increased synthesis of $1,25(OH)_2D_3$ by extrarenal activity of the one alpha hydroxylase enzyme. Subcutaneous fat necrosis is one such condition seen in the neonatal period where indurated painful subcutaneous nodules occur on the cheeks, extremities, buttocks and trunk. Treatment is with hydration and the use of glucocorticoids or bisphosphonates. A similar mechanism occurs when hypercalcaemia complicates tuberculosis or sarcoidosis.

d) Idiopathic Infantile Hypercalcaemia

Affected children typically present after 6 months of age and unlike children with Williams-Beuren syndrome do not have dysmorphic features or cardiac lesions. Some cases are due to mutations in the 24-hydroxylase gene (CYP24A1) leading to failure of degradation of $1,25(OH)_2D_{3.}$. Mutations in the SLC34A1 gene have also been identified in this condition.

e) Williams-Beuren Syndrome

This is due to a contiguous gene deletion on Chromosome 7q11.23 and occurs in 1 in 20,000 births. Hypercalcaemia may be the initial clue to this condition presenting with failure to thrive at a few months of age. The typical dysmorphic features may not be evident at this age but 70% of affected infants will have cardiac lesions particularly supravalvar aortic stenosis. The mechanism for hypercalcaemia is unclear and is usually managed with a low calcium diet and will resolve by 1 year of age.

f) Immobilisation Hypercalcaemia

Acute immobilisation such as due to a head or spinal cord injury may cause hypercalcaemia which typically occurs after a few weeks. This is due to increased bone resorption due to osteoclastic activity causing release of calcium from the skeleton. Hypercalciuria is usually present and may lead to renal stone formation. Treatment is with hydration and the use of bisphosphonates.

Clinical approach to a child with hypercalcaemia:

Age of presentation

In neonates with severe manifestations NSHPT is the most likely diagnosis. It is worthwhile to evaluate maternal calcium status to rule out maternal hypoparathyroidsm. A careful evaluation of calcium intake through supplements and TPN should be done.

In infancy and childhood: if the child is well and thriving with no additional manifestations the most likely cause is FHH. If there is failure to thrive William's Beuren syndrome, Idiopathic Infantile Hypercalcaemia or Hypophosphatasia should be considered.

In adolescence PHPT will be the primary suspicion, and if confirmed multiple endocrine neoplasia should be excluded.

Presence or absence of symptoms: This is an important clinical consideration as if a child is asymptomatic, there is enough time for a diagnostic workup and evaluation of the aetiology and often to watch and wait.

Medications history: Determine exact doses of Vitamin D and calcium taken as supplements.

TREATMENT OF HYPERCALCAEMIA

Stop vitamin D and calcium supplements. Hyperhydration is used to treat symptomatic hypercalcemia as affected children usually have a degree of dehydration due to reduced oral intake and increased losses due to nephrogenic diabetes insipidus. This is effective in promoting natriuresis and decreasing reabsorption of calcium from renal tubules. Furosemide may be used as a temporizing measure to enhance natriuresis.

Symptomatic and severe cases require bisphosphonate infusions. Pamidronate is the drug of choice and is given in a dose of 0.5-1 mg/kg as an infusion over 4-5 hours. Cinacalcet may be used in symptomatic neonatal hypercalcemia or hyperparathyroidism. It is a calcimimetic and inhibits PTH secretion through allosteric activation of the CaSR. Hypercalcaemia due to subcutaneous fat necrosis or other granulomatous conditions is most effectively treated

with corticosteroids which inhibit extrarenal production of 1,25 $(OH)_2D_3$. As a long term measure use of low calcium formula milk may be effective in infants.

In NSHPT or PHPT parathyroidectomy is usually required to control hypercalcemia.

Table 1: Causes of Hypercalcaemia

PTH Dependent	PTH Independent
Neonatal severe HyperPTH	Familial Hypocalciuric Hypercalcaemia Types 1, II & III
Primary HyperPTH	Malignancy eg Leukaemia
Tertiary HyperPTH	Granulomatous Disease eg TB, Sarcoidosis, Subcutaneous Fat Necrosis
MEN Type 1, IIa and IV	Idiopathic Infantile Hypercalcaemia
Mucolipididosis Type II	Williams Syndrome, Adrenal Insufficiency, Hypophosphatasia, Acute immobilisation

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Meet the Expert Session

7:1 – 7:2

The management of a child with Prader-Willi syndrome: from infancy to adulthood

Anita Hokken-Koelega
(Rotterdam, The Netherlands)
Stephany Donze
(Rotterdam, The Netherlands)

- 71: Friday 28 September 2018 at 08:30 -09:30hrs in the Dimitris Mitropoulos Hall

- 7:2 Saturday 29 September 2018 at 14:00 - 15:00hrs in the Banqueting Hall

The management of a child with Prader-Willi syndrome;

From infancy to adulthood

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Introduction

Prader-Willi syndrome (PWS) is a rare genetic disorder, with an estimated incidence of 1:15.000 and a prevalence of 1:50.000 [1]. Hypothalamic dysfunction underlies many of the symptoms of PWS, which include muscular hypotonia, short stature, abnormal body composition with high fat mass and low lean body mass, severe hyperphagia, behavioral problems and cognitive impairment [2,3].

This mini review aims to summarize current management of children and young adults with PWS. Due to space limitations, some issues remain out of the scope of this current mini review.

Diagnosis

PWS is caused by the lack of expression of genes on the paternally derived chromosome 15q11-q13. Genes in this region are physiologically imprinted and silenced on the maternally inherited chromosome. If the paternal alleles are missing, defective or silenced, PWS develops [2,3]. In most cases, PWS is caused by either a paternal deletion or a maternal uniparental disomy (mUPD). In rare cases, imprinting defects or translocations cause PWS (Figure 1).

Figure 1. Genetic causes of PWS

Normal		Genetic abnormalities PWS		
	Deletion	mUPD	Imprinting defect	Translocation
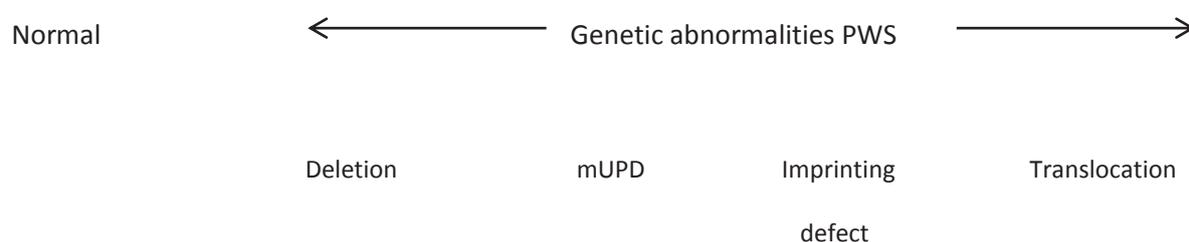
The age of diagnosis has fallen significantly over the last years and the majority of cases are now diagnosed in the first months of life. Before genetic diagnostics became available, PWS was diagnosed using the 1993 Holm criteria [4]. During an international expert meeting in 2006, experts came to agree which clinical features should prompt clinicians to perform DNA testing for PWS (Table 1) [2].

Table 1. Clinical features of Prader-Willi syndrome

Age at assessment	Features that should prompt DNA testing
Birth to 2 years	Hypotonia with poor suck
2 to 6 years	Hypotonia with a history of poor suck Global developmental delay Short stature and/or growth failure with weight gain
6 to 12 years	Hypotonia with a history of poor suck Global developmental delay Excessive eating (hyperphagia, obsession with food) and obesity
13 years - adulthood	Cognitive impairment (usually mild) Excessive eating (hyperphagia, obsession with food) and obesity Hypothalamic hypogonadism Typical behavior (including temper tantrums, obsessive-compulsive features)

From: Recommendations for the Diagnosis and Management of PWS [2]

Testing for PWS is typically performed using DNA methylation analysis, since this is the only technique that can both confirm and reject the diagnosis. If methylation only shows a maternal pattern, PWS is confirmed. Further methods may then be performed to define the genetic subtype.

The most common causes of PWS are a deletion of the PWS region on the paternal chromosome 15 and an mUPD of chromosome 15. We recommend consulting a clinical geneticist for appropriate testing and counseling regarding recurrence risk.

Clinical features

In this chapter we provide a summary of the most important clinical features of PWS. Some features are age-specific and others are not. Children often do not have all features and there is a wide variation in severity.

1. Hypotonia and delayed motor development

Hypotonia, decreased muscle mass and reduced motor activity are almost invariably present in children with PWS. There is a significant motor developmental delay and it is crucial to refer children with PWS to a physical therapist as soon as they are diagnosed, as this improves muscle strength and encourages achievement of developmental milestones.

Even though hypotonia improves with age, it persists throughout the lives of individuals with PWS. Exercise under supervision of a physical therapist should continue to improve functional capabilities and muscle mass and to prevent obesity [5].

> *Hypotonia, decreased muscle mass and delayed motor development are common in PWS. Intensive physical therapy is important, especially in young children.*

2. Feeding difficulties

Most PWS newborns have difficulty feeding and require help with feeding (e.g. tube feeding) to prevent failure to thrive. This is mainly attributed to weakness of the muscles of the mouth, which also contributes to speech development disorders in children with PWS. We recommend consulting a pediatric dietician and a (pre-verbal) speech therapist to support parents of newborn PWS patients.

> *Most infants with PWS require help with feeding. (Pre-verbal) speech therapy is important in case of feeding difficulties, for the transition to solid food and speech and language development.*

3. Body composition, obesity and hyperphagia

As infants grow into children, they develop an increased interest in food, which may progress to uncontrollable eating (hyperphagia). Furthermore, children with PWS have an abnormal body

composition with an increased fat mass and decreased muscle mass, which is already present at birth. There is a disbalance in energy intake and energy expenditure and decreased physical activity and metabolism. Individuals with PWS generally need approximately 60% of calories compared to individuals without PWS.

To prevent children with PWS from developing morbid obesity, we strongly recommend timely start of a well-balanced low-calorie diet, regular exercise and strict supervision and restriction of access to food. We recommend consulting a dietician and a psychologist with expertise on PWS, to advise parents and children on management of food and food-related behavior.

> *Body composition is abnormal with a decreased muscle mass and an increased fat mass. Hyperphagia is common and early restriction of food is important to prevent obesity.*

4. Hormonal disturbances

Adrenal insufficiency

Individuals with PWS have an increased mortality rate, which was estimated at 3% per year under the age of 30 [1]. Studies suggest an increased incidence of central adrenal insufficiency in individuals with PWS, which could contribute to this high mortality rate. There is no current gold standard in terms of the type of test used for adrenal insufficiency in PWS or the frequency of monitoring required. We recommend assessment of adrenal function and supplementation of cortisol during significant illness and surgery.

> *The prevalence of central adrenal insufficiency is increased. In case of surgery, severe infection or severe stress, hydrocortisone stress medication should be considered.*

Growth hormone deficiency

Without GH therapy, the average adult height in boys with PWS is 155-160 cm and in girls 145-150 cm. Serum levels of IGF-I are reduced in the majority of children and spontaneous and stimulated GH secretion vary with different tests and measurements. In 2002 the European Medicines Agency (EMA) authorized somatropin for treating children with PWS, independent of GH secretion. Long-term GH treatment has been shown beneficial and safe for children with PWS, with positive effects on body composition, linear growth, physical strength and cognition [6].

> *Growth hormone has beneficial effects and is a registered treatment for children with PWS.*

Thyroid function

Hypothyroidism has been reported in children with PWS. An increased conversion of free thyroxine (fT4) to T3 has been suggested, which could be enhanced by GH treatment. We recommend to test thyroid function annually and consider replacement therapy if fT4 and T3 are repeatedly low.

> *Yearly evaluation of thyroid function is recommended.*

Puberty and gonadal function

Hypogonadism is a consistent feature in both male and female PWS individuals and hypogenitalism is already present at birth. Most children start puberty, but have incomplete pubertal development and require hormonal replacement therapy for induction or maintenance of puberty, with known benefits to bone health, muscle mass and possible benefits to mental, emotional, and physical well-being [7].

There are case reports of pregnancies in PWS. Sexual counseling and contraceptive treatment should be performed as appropriate [8].

> *Hypogonadism is common in PWS. Hormonal replacement therapy should be applied in case of low estrogen or androgen levels and low or decreasing bone mineral density.*

5. Sleep-related breathing disorders

Sleep-disordered breathing (SDB) is common in PWS, with mainly increased central and sometimes obstructive apneas. Causative factors of obstructive sleep apnea (OSA) include hypotonia, obesity, kyphoscoliosis and hypertrophy of adenoid and/or tonsils. SDB can lead to serious complications, including cor pulmonale, which causes increased morbidity and mortality in PWS.

It is appropriate to screen for sleep-disordered breathing in children with PWS, also before starting GH treatment. We recommend consulting an otolaryngologist in case of snoring and/or suspicion of obstructive apneas, and perform low-threshold adeno-tonsillectomy. Obstructive apneas can significantly increase during upper respiratory tract infections and saturation monitoring during infection needs to be considered, especially in young and obese children.

6. Orthopedic problems

Scoliosis

Scoliosis is defined as an angle above 10 degrees between the two vertebrae that are most tilted towards each other. The prevalence of scoliosis in children with PWS increases with age, with a prevalence up to 80% in children older than 10 years of age [9]. We recommend annual clinical evaluation of scoliosis and x-rays of the spine at least every other year from the age of 2 years up to attainment of adult height to detect progression of scoliosis. We also recommend consulting an orthopedic surgeon at the age of 8 years and at least once during puberty and in case of a Cobb angle > 15 degrees.

Treatment of severe scoliosis should be performed in a multidisciplinary team with experience regarding scoliosis in neuromuscular disorders.

Scoliosis, congenital hip dysplasia and pes planus are prevalent in PWS and require regular evaluation and care by an orthopedic surgeon, physical therapist and a physical medicine and rehabilitation physician.

7. Cognitive disorders

The intelligence quotient (IQ) of individuals with PWS varies from 50 to 85, with 25% of patients having an IQ above 70. Recent studies have shown that GH treatment improves IQ during long-term GH treatment [10].

Individuals with PWS have an IQ between 50 and 85, which seems to improve during long-term GH treatment.

8. Behavioral problems

In the first years of life, children with PWS are friendly and sociable. Conjointly with the change in feeding behavior, there is often a change in their behavioral phenotype. Behavioral challenges range from very mild to very severe and each individual may display different behavior, depending on age, external environment and emotional development. The most common types of behavioral difficulties include temper tantrums, stubbornness and resistance to change, mood changes, skin picking and manipulative behavior. Obsessive-compulsive and autistic features are common [11,12].

Clinicians should bear in mind that a sudden increase in behavioral problems could be attributed to an underlying medical problem (e.g. constipation, infection) or increased stress due to changes in their environment. Support from a psychologist and/or psychiatrist can improve quality of life of patients and their caregiver(s).

> *Behavioral difficulties are common and require an integrated approach with attention for medical, psychological and environmental factors.*

9. Psychiatric Disorders

Adolescents with PWS can develop psychiatric symptoms, including psychosis, oppositional defiant disorder (ODD) and obsessive compulsive disorder [12]. Active, extravert children and children with mUPD have an increased risk of developing psychotic symptoms during adolescence. Passive and introvert children have an increased risk of developing bipolar disorder during adolescence and adulthood [11].

> *There is an increased risk of developing affective and psychotic disorders.*

Management

1. Multidisciplinary management

It is of utmost importance that individuals with PWS receive support from a highly specialized multi-disciplinary team. Because PWS is rare and is characterized by several complex health issues, follow-up in a PWS expert center is indispensable to make sure individuals with PWS receive the best possible care. A suggested visiting scheme is attached to this mini review.

2. Growth Hormone treatment

Treatment with GH in children with PWS is approved by the European Medicines Association in 2002 and is applied by pediatric endocrinologists for more than 15 years. All children with genetically proven PWS, regardless of stimulated or spontaneous GH secretion, are eligible for GH treatment. Current clinical practice is to start GH treatment in conjunction with dietary and lifestyle interventions soon after diagnosis and should be continued for as long as demonstrated benefits outweigh the risks [13].

Contra-indications for GH treatment:

- BMI > +3 SDS
- Uncontrolled diabetes mellitus
- Severe sleep-related breathing disorders
- Active cancer
- Psychosis

Evaluation before starting GH treatment:

- Polysomnography to exclude/ demonstrate sleep-related breathing disorders
    - In case of obstructive apneas children should be referred to an otolaryngologist with low-threshold for performing adenotonsillectomy in case of OSAS and/or hypertrophy of adenoids/tonsils.
    - In case of more than 5 central apneas per hour children should be referred to a neurologist.
- Children with scoliosis (>15°) should be evaluated by an orthopedic surgeon

Effects of GH

Height and body composition: GH treatment in children with PWS has positive effects on body composition and height and has substantially changed the phenotype of children with PWS [6].

Psychomotor development: In the last decade, the knowledge of the clinical presentation of PWS has increased and diagnosis is nowadays made at an early age, making early start of GH treatment possible. Several studies have shown that early start of GH, results in more improvement in psychomotor development [14].

Muscle strength and physical activity: muscle strength and physical condition improve with GH treatment and parents report that their children are more active in daily life.

Cognition and adaptive functioning: certain cognitive skills improve during GH treatment, while cognitive functioning of GH-untreated PWS children deteriorates [10]. GH maintenance therapy may prevent or slow down the progression of behavioral problems in PWS individuals [15]. An earlier start of GH treatment, leads to better adaptive skills on the long-term [16].

> *GH treatment has a positive effect on body composition, height, psychomotor development, muscle strength, cognition and adaptive functioning.*

Safety of GH

Sleep-related breathing disorders: A recent review concluded that GH can be safely administered, providing that sleep-related breathing disorders are appropriately monitored and treated [17].

Scoliosis: GH treatment does not negatively influence the onset and progression of scoliosis [18].

Carbohydrate metabolism and cardiovascular risk factors: GH treatment is associated with lower insulin sensitivity that recovers after cessation of GH. Studies on the safety of long-term GH treatment in children with PWS are reassuring without negative effects of GH on insulin resistance and cardiovascular risk factors [6].

Severe illness or surgery: The Growth Hormone Research Society advised to temporarily stop GH treatment during complicated surgery and severe illness in all patients (GH Research Society 2001).

GH in adults with PWS

Studies have shown that GH treatment is beneficial for adults with PWS, with a sustained improvement of body composition when GH is continued, and a deterioration of body composition when GH treatment is discontinued after attainment of adult height [19].

However, as most adults with PWS do not fulfil the consensus criteria for adult growth hormone deficiency, they currently cannot be treated with GH. There is a need for the registration of GH treatment for adults with PWS, regardless of the presence of adult GHD.

Studies have shown that GH treatment has positive effects on body composition and health profile in adults with PWS.

3. Future treatments

Oxytocin
The number of oxytocin-expressing neurons in the hypothalamus of individuals with PWS is decreased. Oxytocin is known to be involved in food intake, body weight and social skills. Recent studies on the effects of oxytocin in (pre-pubertal) children with PWS suggest positive effects on social and food-related behavior without side effects or adverse events [20]. Besides, oxytocin resulted in an improvement in sucking and swallowing in infants with PWS [21]. However, more studies are required to evaluate the effects of oxytocin in children and young adults with PWS.

Other
Several other treatment options for PWS are currently being investigated.

Unacylated ghrelin analogues

The appetite-stimulating hormone ghrelin has an acylated and an unacylated form. Acylated ghrelin (AG) is known to stimulate appetite and unacylated ghrelin (UAG) improves glycemic control and suppresses AG. A recent study reported an increased AG/UAG ratio in individuals with PWS compared to controls. Also, individuals with weight gain and/or hyperphagia had a higher AG/UAG ratio than individuals without weight gain and/or hyperphagia [22]. It is hypothesized that UAG-analogues could alter AG/UAG ratio and reduce appetite in individuals with PWS.

Glucagon-like peptide-1 analogues

Studies have shown that Glucagon-like peptide (GLP)-1 analogues influence appetite, body weight and glycemic control in patients with diabetes mellitus type 2 and obesity. Currently, studies are being performed on the efficacy and safety of GLP-1 analogues in obese individuals with PWS.

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Suggested visiting scheme

Overview of contacts in PWS Expert Center * = if indicated					
	0-1 year	**1-4 years**	**4-12 years**	**Puberty**	**Transition period**§
Pediatric endocrinologist	6-monthly	6-monthly	6-monthly	6-monthly	Every year
Pediatric dietician	At least once	Every year	Yearly up to 8 years, every other year thereafter	At age 12 and 16 years	*
Physical therapist	At least once	Every year	At age 6 and 10 years	At age 14 years	*
Psychologist	At least once	Every year	Every other year	Every year	Every other year
Orthopedic surgeon	*	*	At least once at age 8 years	At least once	*
Ophthalmologist	*	At least once	*	At least once	*
Otolaryngologist	*	At least once	*	*	*
Pediatric urologist	If there is cryptorchidism	*	*	*	*
Cardiologist	*	*	*	*	At least once
Psychiatrist	*	*	*	*	*
Endocrinologist					6-monthly

Overview of contacts local hospital * = if indicated					
	0-1 year	**1-4 years**	**4-12 years**	**Puberty**	**Transition period**§
Pediatrician	6-monthly	6-monthly	6-monthly	6-monthly	Every year
Speech therapist	Weekly	Weekly	*	*	*

Physical therapist	Weekly	Weekly	*	*	*
Physiatrist	*	*	*	*	*
Dentist / orthodontist	*	From 2 years onwards: 6-montly	6-monthly	6-monthly	6-monthly

Overview of examinations in Expert Centrum or local hospital * = if indicated					
	0-1 year	**1-4 years**	**4-12 years**	**Puberty**	**Transition period[§]**
Anthropometrics	3-monthly	3-monthly	3-monthly	3-monthly	6-monthly
Physical examination (incl. pubertal stage)	3-monthly	3-monthly	3-monthly	3-monthly	6-monthly

	0-1 year	**1-4 years**	**4-12 years**	**Puberty**	**Transition period**
Laboratory assessments[**]	Every year and *	Every year and *	Every year and *	Every year and *	Every year and *
X-ray of hand (bone age)	Before starting GH	Every other year	Every other year, Every year from 8 years onwards	Every year	Every year up to attainment of adult height
X-ray of spine (scoliosis?)	*	Every other year from 2 years onwards	Every other year and *	Every other year and *	Every other year up to attainment of adult height and *
Dexa-scan**	Every year	Every year	Every year	Every year	Every year
Polysomnography	Before starting GH	Before starting GH and *	*	*	*
Central adrenal insufficiency test	#	#	#	#	#
ECG, echo cor	*	*	*	*	At least once

§ *Transition period in PWS lasts from approximately 17 to 25 years.*

** *At 6 months after starting GH an extra laboratory assessment and Dexa-scan should be performed.*

Consider formal testing for central adrenal insufficiency and inform patients and their parents about signs and symptoms of adrenal insufficiency. In case of surgery, severe infection or a very stressful condition, we recommend to give hydrocortisone stress medication, unless central adrenal insufficiency has recently be excluded.

Meet the Expert Session

8:1 – 8:2

Psychology of childhood diabetes: How to motivate children and families with T1D

Karin   Lange (Hannover, Germany)

- 8:1 Friday 28 September at 08:30 - 09:30hrs in the Nikos Skalkotas Hall

- 8:2 Saturday 29 September at 14:00 - 15:00hrs in the Dimitris Mitropoulos Hall

Prof. Dr. Karin Lange
Hannover Medical School
Medical Psychology

Clinical practice paper

Psychology of childhood diabetes: how to motivate children and families with type 1 diabetes

Type 1 diabetes in childhood is a family project challenging all members 24h/365 days a year (1, 9). More than 99% of the hours of a year parents and children have to manage the diabetes therapy on their own responsibility. They have to perform a multitude of self-management tasks responding to changes in physical activity, food intake, emotional well-being and physiology. In addition parents have to combine their role as loving carer with role of the responsible 'diabetologist' of their child (10, 12). Thus, personalized structured education and psychosocial support for all family members are the keystones of diabetes care, and self-management education is the key to a successful metabolic outcome and child's age appropriate psychosocial development (2, 10, 11). Current pediatric guidelines provide comprehensive guidance on the various aspects of education and offer general and organizational principles of education, detailed curricula at different ages and stages of diabetes, and recommendations on models, methods, and tools to attain educative objectives (7, 11).

Diabetes education is an interactive process that supports families to acquire and apply the necessary knowledge to develop confidence to manage their life with diabetes. Age-specific curricula are based on psycho-educational principles and combine practical education with problem solving tasks, goal setting, communication skills, motivational interviewing (4), family conflict resolution (3,12), support of self-efficacy and psychosocial adaptation (9). Lifelong diabetes management requires regular continuing qualified education: evaluated education programs for initial in-patient and follow-up outpatient education, and structured trainings for educators on diabetes care, child psychology, and pedagogics (9, 10). To sustain the high level of self-management needed to effectively manage type-1-diabetes over the long term, children, adolescents and their families need ongoing diabetes-self-management support (7, 15).

Several family factors including levels of family cohesion, agreement about diabetes management responsibilities, and levels of supportive and collaborative problem-solving behaviours influence treatment regimen adherence and glycaemic control of children and adolescents (1, 2). Family conflict is associated with lower adherence to insulin therapy and poor glycaemic control. Therefore, general family functioning and diabetes-related functioning should be assessed especially when there is evidence of cultural, language or family problems or difficulties in adjustment to diabetes. Accordingly current guidelines highlight the critical importance of integration of psychological and social aspects in pediatric diabetes care and education (2, 10).

But even for families well adapted to the daily work of managing their child's disease the ongoing type-1-therapy is a psychological challenging task: due to unexpected glucose fluctuation they regularly have to cope with frustration and feelings of helplessness and guilt; they suffer from fear of severe hypoglycaemia and ongoing worry about their child's future and possible complications of diabetes due to elevated HbA1c-levels. Especially mothers of young children are often affected by

symptoms of anxiety, depression or burn-out (2, 15). Teenagers and adolescents with type 1 diabetes appear to have a greater incidence of depression, anxiety, psychological distress and eating disorders compared to their healthy peers (2). Several young people with type 1 diabetes are overwhelmed by the requirements for self-discipline, impulse control, diabetes self-management, striving for autonomy from parents and coping with age-appropriate developmental tasks (8, 13). Because self-management takes place in their daily lives and not in clinical or educational settings, young people need assistance to formulate a plan to find resources that may support their ongoing diabetes self-management. Ideally, diabetes team members will work with adolescents to identify such resources and, when possible, track those that have been effective. In addition differences in behaviours, health beliefs, and culture as well as the emotional response to diabetes can have a significant impact on how young people with diabetes understand their illness and engage in self-management.

Health Action Process Approach – a concept to explain diabetes self-management

Among others the Health Action Process Approach (HAPA) is a theoretical construct to explain the mechanisms of health behaviour change that have been found useful in research on people with chronic illness, disability, and diabetes (14). This self-regulation framework may also serve as a backdrop to analyse the components that motivate people with diabetes and their families for ongoing self-management therapy (Figure 1).
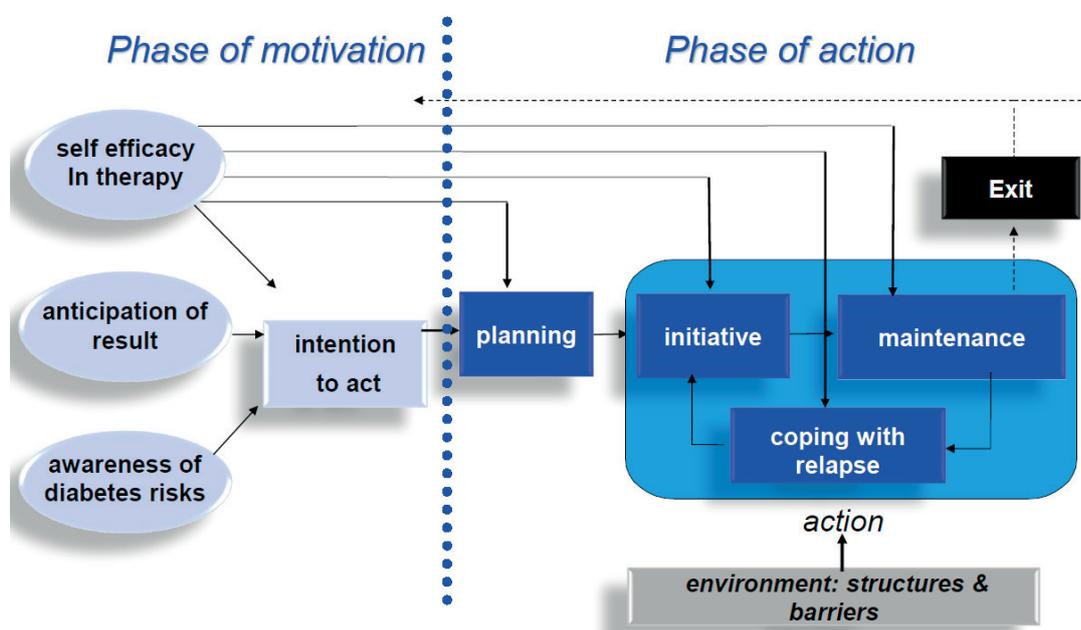

Figure 1: Self-regulation framework (HAPA) explaining the social-cognitive processes of behaviour change (14) adapted to the everyday challenges of young people with type-1-diabetes

Core element of the HAPA is the distinction between the phase of goal setting and the phase of goal pursuit. In the motivational (goal-setting) phase diabetes-specific risk perception, outcome expectancies, and experienced self-efficacy are seen as predisposing factors for any activity or behaviour change to cope with the diagnosis of type-1-diabetes. In the subsequent action phase self-efficacy is regarded as being influential for planning, action control, and maintenance of ongoing diabetes-self-management. In the first phase of coping with diabetes all family members form an intention to cope with the disease, in the second phase they start to actively change their behaviour, e.g. check glucose levels, adapt insulin doses to physical activity, and count carbs. This mediator model serves to explain the social-cognitive processes in health behaviour change as it is necessary for people newly diagnosed with type-1- diabetes.

Following this model, three stages can be distinguished to segment young people with diabetes and their families for individualized interventions to strength their motivation and adherence to insulin therapy. Identifying them as pre-intenders, intenders, or actors offers the opportunity to match theory-based diabetes information, support and treatment to specific groups of young people. In the workshop on clinical cases this theoretical model will be used to develop tailored interventions to sustainably motivate children, adolescents and parents dependent from being characterized as being pre-intender, intender or actor.

Clinical cases

1) At diagnosis of type-1-diabetes in a 5-year old boy parents need in this first "phase of motivation" basic information on their child's risk, the future perspectives (outcome expectation) and their ability and chance to support their son (self-efficacy). The same information has to be given to the boy in an age-appropriate way. On this background giving the diagnosis and building a trustful relationship becomes a most relevant first step of diabetes long-term care. These first 30 minutes of diabetes care and doctor-patient communication will be discussed in detail. During the first in-patient education course all family members need sufficient, honest, and realistic information about the child's future perspectives, the need of insulin therapy, and about acute complication. The parents should be protected from great anxiety, e. g. fear of hypoglycemia, and supported to develop a hopeful future perspective. Furthermore, realistic and achievable therapeutic goals should be developed. Diabetes-teams listen on reports of helplessness and guilt, and support all family members to develop a feeling of security and self-efficacy. Via the comprehensive practical training of all 'survival skills' for everyday life with diabetes educators and other team-members support feeling of self-efficacy as well as positive coping among parents and child; all activities and measures of the different multi-professional team members have to follow common therapeutic goals and a shared holistic approach.

2) Especially parents of very young children (< 4 yrs.) with typ-1-diabetes suffer from (un-)realistic fear of hypoglycemia and extreme diabetes distress. Several successful arguments, practical tools and psychotherapeutic strategies will be addressed to support parents to better cope with their anxiety and to reduce their parenting stress (12) Furthermore tools for effective use of CGM in children and their parents are presented (5,6), e.g. worksheets on realistic expectations; discussion of parents' and children's emotional reactions on alerts and unexpected glucose variation; cognitive behaviour techniques to prevent from overreaction on hypo alarms; step-by-step introduction of

different alarms to prevent children, parents and other carer from overload; worksheets to support positive parent-adolescent cooperation ('coaching contract').

3) Concerns, challenges and opportunities common to adolescents with diabetes are addressed in the third case report, e.g. accepting the critical role of continued parental involvement and yet promoting independent, responsible self-management appropriate to the level of maturity and understanding, emotional and peer group conflicts, problem solving strategies for dealing with dietary indiscretions, illness, hypoglycemia, blood glucose fluctuation due to puberty, sports, smoking, alcohol, drugs, reproductive and sexual health and family planning.

As young people with chronic poor metabolic control, including recurrent DKA, are more likely to have underlying psychosocial problems or psychiatric disorders than teenagers in stable metabolic control their challenges and chances for behavior change will be addressed on the background of the HAPA construct and the method of motivational interviewing. With the latter technique 1) personally relevant motives are identified, 2) ambivalences (conflicts between courses of action) are articulated and resolved, 3) self-confidence is supported by focusing on former successes, resources, and social support, 4) adolescent's own self motivational statements (problem recognition, concern, desire and intention to change) are selectively reinforced. This may help in clarifying adolescent and parental goals and resolve ambivalence about intensification of insulin therapy.

To prevent deterioration of metabolic control in adolescence interventions for patients and families, e.g. training parents in effective behaviour management and parenting skills, can be offered at key developmental phases. This coaching for parents emphasize appropriate family involvement and support in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycaemic control among teenagers (11,12).

As for parents of younger children an education program for adolescents planning to start with rtCGM (SPECTRUM) (5) was developed to motivate young people to use the system successfully on the long run. In addition to a comprehensive technical introduction several worksheets address realistic expectations for adolescents and parents, practical aspects of CGM in school, discussion of parents' and adolescents' emotional reactions on alerts and unexpected glucose variation, cognitive behaviour techniques to prevent from overreaction on hypo alarms, step-by-step introduction of different alarms to prevent adolescents from overload, and worksheets to support positive parent-adolescent cooperation ("coaching contract"). On this way SPECTRUM strives for qualified, structured information on CGM for young people with type-1-diabetes and their families and also for supporting their motivation to sustainably use rtCGM and improving their quality of life.

Conclusion

- Motivation for type-1-diabetes therapy is highly individual and depends from child's age, educational level, psychological wellbeing, cohesion and support of the family, the ability to cope with frustration, impulse control and the ability to understand complex interactions.
- All interventions to support motivation of young people have to be tailored to their individual wishes, needs and barriers.
- Nevertheless, there are three core factors predicting patients' motivation: a realistic risk perception, realistic and reachable treatment goals and the experience of self-efficacy.

- Structured diabetes education and long-term care can support the sense of self-efficacy by comprehensive skill-training, self-management education and - last but not least - by focusing on the strength and the successes of young people with diabetes and their parents.

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