Shropshire Community Health NHS Trust

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Who is the document aimed at?	Medical professionals working with children and young people in Shropshire Community Trust
Owner	Dr M. Ganesh, Dr S.Saran, Dr Raveendran & Dr Eltahir
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Amendments History		
No	Date	Amendment
1	V1 April 2014	New policy
2	V2 July 2017	Discussed at peer meeting and alterations made and accepted Birmingham Women's Genetic department permission to use PIL SATH informed re updated guidelines and increased risk of VTE SSSFT CAMHS lead informed re updated guideline
3	V3 Nov 2020	General review and discussed with community paediatrics team
4		
5		
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Contents:

Prader Willi Syndrome:
Management and Health Surveillance Guidelines

1. Introduction

Prader Willi Syndrome (PWS) is a rare inherited genetic condition that has a recognisable set of physical findings and can lead to cognitive, neurological, endocrine and behavioural problems. This can lead to complex management issues for patients, carers, families and medical professionals.

2. Purpose

The purpose of this guideline is to aid medical professionals working in Shropshire Community Health NHS Trust to be able to identify patients with PWS and investigate, diagnose and treat this condition effectively within a multi-professional environment.

3: Definitions.

Meiotic non disjunction: The failure of homologous chromosomes to separate equally during meiosis cell division resulting in daughter cells with improper chromosome content
Imprinting: Phenomenon where certain genes are expressed depending being either maternally or paternally derived.
Uniparental Disomy: Usually 1 copy of a gene is inherited from each parent. In uniparental disomy 2 copies of a gene are inherited from one parent and none from the other. This is usually due to meiotic non disjunction. In PWS both genes on chromosome 15 will be inherited from the mother with no copy from the father.
Hyperphagia: excessive hunger or appetite.

4. Duties

4.1 Chief Executive

The Chief Executive has ultimate accountability for the strategic and operational management of the Trust, including ensuring there are effective and appropriate processes in place for the medical management and health surveillance of children with Prada Willi Syndrome.

4.2 Director of Nursing & Medical Director

The Director of Nursing & Medical Director have responsibility for ensuring that children with PWS are offered appropriate medical management and health surveillance checks and to support patient safety at all times.

4.3 Service Managers

Service Managers are responsible for the day to day operational management and coordination of the medical management and health surveillance of children with PWS in accordance with clinical guidelines and to be aware of MDT responsibilities in managing these patients.

4.4 All Clinical Staff

Clinical staff is key essential members of the MDT in ensuring that children with PWS are managed appropriately as per national/ local guidelines and are offered regular health surveillance checks. All clinical staff are required to comply with this guideline

and to report any adverse care related issues to their line manager and to complete a Datix incident report in line with Trust Incident reporting policy.

5. Body of Policy

5.1 Genetics

PWS is caused by a lack of expression of paternally derived imprinted genes on chromosome 15q11-q13. PWS was the first condition proved to be caused by the phenomenon of genetic imprinting.
Approximately 70% of cases are caused by deletion of genes on chromosome 15q11-q13. 28% of cases are due to maternal uniparental disomy caused by meiotic non disjunction.
Less than 1% of patients with PWS have deletions of this chromosome related to the imprinting centre which carry a risk of recurrence.

5.2 Epidemiology

Recent studies have shown that the relative population prevalence in Europe and Australia is 1:50,000, and 1: 45,000 in the UK.

5.3 Clinical manifestations

PWS has a great range of signs and symptoms and there are varied causes of morbidity and mortality throughout the natural history of the condition. Affected children uniformly have neonatal hypotonia and feeding problems associated with poor weight gain. As the patient ages a second phase of symptoms ensue characterised by hyperphagia, obesity and behavioural problems.
Without adequate control of this hyperphagia and behavioural problems the child will develop long term sequalae such as hypertension, diabetes mellitus, obstructive sleep apnoea and right sided heart failure.

A more comprehensive list of clinical features is listed in the following table:

Neonatal

- Breech position
- Reduced foetal activity
- Polyhydramnios

Growth

- Short stature
- Failure to thrive in infancy
- Central obesity

Head and neck

- Narrow bitemporal diameter
- Almond-shaped eyes
- Strabismus
- Up-slanting palpebral fissures
- Myopia
- Hyperopia
- Thin upper lip
- Small-appearing mouth
- Down-turned corners of mouth
- Thick, viscous (reduced) saliva
- Enamel hypoplasia
- Early dental caries
- Dental crowding and malocclusion

Ocular

- Strabismus
- Nystagmus
- Cataracts (rare)
- Retinal hypopigmentation
- Foveal hypoplasia
- Hyperopia
- Myopia

Respiratory

- Hypoventilation
- Obstructive sleep apnoea
- Central sleep apnoea

Gastrointestinal

- Feeding problems in infancy
- Gastroesophageal reflux
- Increased vomiting

Genitourinary

- Small penis
- Scrotal hypoplasia
- Cryptorchidism
- Hypoplastic labia minora
- Hypoplastic clitoris

Skeletal

- Osteoporosis
- Osteopenia
- Scoliosis
- Kyphosis
- Small hands and feet
- Narrow hands with straight ulnar border
- Clinodactyly

Skin, nails, hair

- Hypopigmentation
- Blonde to light-brown hair
- Frontal hair upsweep
- Skin picking

Neurologic/ developmental

- Severe neonatal hypotonia that improves with age
- Poor neonatal suck and swallow reflexes
- Poor gross motor coordination
- Poor fine motor coordination
- Mild-to-moderate Learning difficulties.
- Increased risk of seizures
- Global developmental delay
- Speech-articulation problems
- Hyperphagia

Sleep

- Snoring/obstructive sleep apnoea
- Central apnoea during sleep
- Excessive daytime sleepiness
- Early-morning waking
- Night-awakening for food-seeking

Voice

- Hypernasal speech
- Weak or squeaky cry in infancy

Endocrine

- Hyperinsulinemia
- GH deficiency
- Hypogonadotropic hypogonadism
- Diabetes mellitus (type 2)

Behaviour/mental health

- Temper tantrums
- Difficulty with transitions
- Stubbornness
- Obsessive behaviours
- Perseverant speech
- Obsessive-compulsive disorder
- Psychosis
- Elopement

Miscellaneous

- Temperature instability
- High pain threshold
- Unusual skill with jigsaw puzzles
  Also refer to appendix 1: unique features

5.4 Clinical Diagnosis

The diagnosis of a child with possible PWS is usually apparent from the clinical phenotype however genetic testing is becoming more freely available and is considered the gold standard of diagnosis. There are widely agreed situations when genetic testing of children for PWS is deemed appropriate. This is outlined in the following table:

Age at assessment	Features sufficient to prompt DNA testing
Neonatal period	• Neonatal hypotonia • Poor feeding
2–6 yr	• Global developmental delay • Short stature and/or growth failure associated with accelerated weight gain
6–12 yr	(hypotonia often persists) • Global developmental delay • Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
13 yr through adulthood	• Cognitive impairment, usually mild • Learning difficulties • Hypothalamic hypogonadism • typical behaviour problems (Including temper tantrums and Obsessive-compulsive features)

5.5 Management

Management of children with PWS is complex and involves a multi-disciplinary approach. There are different things to focus on depending on the age of the patient.

a) Neonatal period

- Most neonates with PWS are susceptible to faltering growth.
- The main problem in the neonatal period is hypotonia and poor suck leading to feeding difficulties and failure to thrive with requirement of tube feeding.
- Dietetic input is mandatory

b) Cryptorchidism

- This occurs in over 80% of boys with PWS.
- As with children with cryptochordism without PWS, orchidopexy should be performed by year 2 of life, to avoid the small chance of testicular cancer if orchidopexy was not performed. It is also a much more technically demanding procedure after the onset of scrotal hypoplasia and obesity.

c) Hypotonia

- Children with PWS syndrome display muscle hypotonia, decreased muscle mass, general developmental delay and a reduced number of activity dependent type 2 muscle fibres.
- Early involvement of physiotherapy is required, although there is no definitive evidence that physiotherapy improves gross motor delay or improves time to sit or walk.
- Continuing exercise is necessary to combat ongoing reduction in muscle mass as hypotonia persists into adulthood.

d) Growth and Growth hormone treatment

Paediatric endocrinologist involvement is essential from as early as 3 months of age, because the early start of growth hormone therapy (even < 6 months old), can significantly increase lean body mass (earlier walking) and therefore improve body composition, reducing the risk of obesity, metabolic syndrome and type 2 diabetes

- Pre and postnatal Growth restriction
- Short stature due to growth hormone deficiency and lack of pubertal growth spurt.

- There is no evidence that GH status is directly linked to height velocity therefore GH testing before starting treatment is not essential but can be helpful.

The aims of GH treatment in children with PWS are:

- to improve childhood growth velocity
- to increase final adult height
- to improve body composition.

Most studies evaluating the use of GH test the dose of 0.6-1mg/m2/day and current evidence shows this significantly improves these parameters in the first year following starting treatment.

There are positive effects on body composition and bone mineral density once maximal height velocity has been achieved.

Hypothyroidism is common in children with PWS and measurement of TSH, free T3 and free T4 should be done pre and post commencement of GH therapy.

There is established evidence that starting GH therapy before two years of age is of benefit. However there is increasing evidence that starting therapy at 6-12 months may be of even more beneficial. Not only in terms of final adult height and improving bone density, but also improving the developmental skills of the child (In improving the developmental milestones.)

Monitoring of children in preparation for, and whilst on GH therapy should consist of the following:

Before starting GH treatment In improving the developmental milestones.

1) Genetic confirmation of PWS
2) Evaluation of IGF-I status and, if possible, GH status
3) Nutritional evaluation
4) Prior control of food environment is vital, especially in obese children
5) Sleep Study and ENT evaluation
6) OGTT (in older children)
7) Family instruction on GH treatment
8) Scoliosis evaluation consider x-ray
9) Evaluation of hypothyroidism (TSH, free T4, free T3)
10) Bone age study (not in very small infants)
11) Weight, height, height velocity and BMI evaluation

On GH treatment

1) Regular clinical assessment of height, weight, BMI, body composition
2) ENT assessment and polysomnography within the first 6 months
3) If development or worsening of sleep-disordered breathing, snoring, or enlargement of tonsils and adenoids, ENT assessment +/- polysomnography
4) Orthopaedic assessment for scoliosis
5) Regular bone age determination
6) Monitoring for Thyroid function and IGF.

Cessation of GH treatment

1) Uncontrolled progression of obesity
2) Continued worsening of glycaemic control
3) Continued worsening of sleep-disordered breathing
4) Attainment of final height (but because there are potential benefits in adults on
5) body composition, peak bone mass, cognition, and quality of life, reassessment of persistent GH deficiency, and replacement with adult doses may be warranted)

e) Management of puberty

Paediatric endocrinologist role is essential as there is no universally agreed treatment regimen for induction of puberty in children with PWS.

- Hypogonadism (central and peripheral) is almost a universal problem in both boys and girls with PWS.
- Most people with PWS will either have delayed, incomplete or absent puberty.
- There can be isolated premature pubarche, and there is also a small incidence of precocious puberty in males.
- At some point almost all children with PWS will require sex steroid therapy for induction, promotion or maintenance of puberty.
- Sex steroid therapy is also very important for bone mineralisation (bone density).
- In children with significant learning difficulties hygiene issues surrounding puberty can be an enormous problem and need to be discussed with carers. However learning difficulties should not be seen as a contraindication for usual treatment to stimulate normal puberty

f) Sleep Related Breathing Disorders

- Both obstructive sleep apnoea (OSA) and centrally derived apnoea and hypoventilation occur in PWS.
- OSA can occur due to hypotonia, obesity, upper airway dysfunction, kyphoscoliosis and adenotonsillar hypertrophy.
- OSA leads to a variety of complications such as systemic hypertension, pulmonary hypertension, cor pulmonale and cardiovascular disease.
- Up to 75% of PWS can have problems with sleep disordered breathing (SDB) with frequent hypoxic events, sometimes complicated by an abnormal central ventilation response. Growth Hormone administration exacerbates SDB in these patients.
- Sleep disordered breathing can cause cognitive deficiencies, behavioural problems, poor school performance and psychiatric disorders.

Recommendation:

- Paediatric respiratory specialist is required to manage apnoea.
- All patients with PWS should be referred for an annual inpatient overnight oximetry WITH capnography.
- PWS patients due to commence Growth Hormone should have a pre-therapy inpatient polysomnography with capnography study.
- Referral to be made for an overnight oximetry, or a Paediatric Respiratory Team.

g) Orthopaedic Management

- Scoliosis and kyphosis are common in children with PWS due to hypotonia and obesity (relative prevalence of between 30 and 70%).
- Weight control is also required for reducing the risk of scoliosis.

- Assessment for scoliosis is needed before starting growth hormone replacement, as scoliosis generally worsens in children who are receiving growth hormone replacement.

- Worsening scoliosis is not an absolute indication to stop GH therapy.

- Orthopaedic referral is indicated in severe early onset disease as well as children nearing skeletal
- Complications of surgical management of scoliosis are more common in children with PWS with a high risk of paraplegia (20%) and of major complications (30%, deep infections, pneumonia).

h) **Management of hyperphagia/ obesity**

- Early education for parents regarding the development of hyperphagia is essential in managing obesity and future complications
- Psychological support for children with PWS and their parents/ carers.
- Early onset of calorie controlled diet with restriction to the access of food and money to buy food.
- Dietician referral to support dietary control.
- Regular exercise, with appropriate support / support groups
- There is no evidence to support the use of appetite inhibitor, somatostatin analogues, and bariatric surgery.
- Type 2 diabetes mellitus is common in patients with PWS, occurring in around 20% of cases with a mean time of onset around 20 years, treatment should follow current national guidance.
- It should be noted that patients with PWS and diabetes need routine health surveillance related to their diabetes, (retinopathy screening, nephropathy screening etc) as well as health surveillance related to their PWS.

5.6 Ethical considerations

The support of vulnerable people; whether children or adults, is an essential core value to the medical profession. However this involves the careful balance of respecting an individual's autonomy and to avoid exploitation, harm and potential abuse.

Parents need to be educated early about the prospects of hyperphagia and the risks of developing obesity and obesity related problems. Once this education has occurred parents have a duty to act in the child's best interest to avoid these problems as much as is conceivably possible. It's therefore difficult to control patient's decision making, especially as they gain age and increasing autonomy.

It should be noted however that patients with PWS almost always have reduced satiety, and poor control over their eating disorder. Also metabolic complications of obesity are almost certainly of a poorer prognosis in PWS.

Therefore early death is likely without control of these problems from an external source.

There is good evidence that control of access of food and to money to buy food is essential for good long term prognosis. Therefore systems need to be in place for families and carers to put these systems into place with support from the medical professionals. These systems should have the agreement of the patient as much as is possible.

Problems occur when patients do not agree to such external controls. It can be argued that patients with PWS do not have capacity to make decisions related to food and diet and that we therefore have a duty of care to put these systems into place as much as is possible.

In reality this will involve intensive discussion and negotiation with the patient and carers over a period of time.

A multi-disciplinary team is involved with patients with PWS:
Shropshire Community Health NHS trust:

- Community Paediatrician-Lead clinician
- Dietician
- Physiotherapist
- Psychologist
- Speech and language Therapy

Shrewsbury and Telford NHS Trust:

- Neonatologist
- Paediatric endocrinologist
- Gynaecologist / urologist
- Paediatric Cardiologist
- ENT specialist
- General Surgeon (for orchidopexy)
- Respiratory paediatrician
- Dentist
- Ophthalmologist
- Paediatric Gastroenterologist

Birmingham Women's Hospital:

- Clinical genetics department,

SSSFT:

- CAMHS

Robert Jones and Ages Hunt Hospital:

- Orthopaedic surgeon

Local Authority:

- Social worker

6. Consultation

The guideline has been discussed by the community doctor's team (Dr M Ganesh, Dr S Bush, Dr G Minnaar, Dr H Unsworth and Dr D Short).
Both the neighbouring trusts involved in the care of children are informed about the update of this guideline (Alex Critchell, SSSFT and Dr Naeem Ayub, SATH)

7. Dissemination and Implementation

Guideline will be available in hard copy at the Community doctor office and on the trust internet.

8. Monitoring Compliance

Guideline will be audited but as incidence is infrequent cohort will be small and data will be collected over a few years from initiation of this guideline.

9. References

Recommendations for the Diagnosis and Management of Prader Willi Syndrome. A.P. Goldstone et al J Clin Endocrinol Metab November 2008 93(11) 4183-4197

Up To Date, epidemiology and genetics of Prader Willi syndrome, https://www.uptodate.com/contents/epidemiology-and-genetics-of-prader-willi-syndrome#H3

https://www.nhs.uk/conditions/prader-willi-syndrome/symptome

10. Associated Documents

Guidelines for the Public Health Nurse Team for the Management of Growth Measurements in School Age Children 1947-40658

11. Appendix:

Prader Willi Syndrome- Unique features

Temperature instability (Lack of fever does not rule out serious infection)	Cortisol Deficiency (May have underlying cortisol deficiency and need hydrocortisone. check with the Endocrine team)
High pain threshold (May not complain of pain despite of serious injures including fractures)	Hypothyroidism
Lack of vomiting (Vomiting should be taken up seriously it may be a pre terminal sign)	Vit D deficiency
Gastroparesis	Anaesthesia (Thick secretions, prolonged drowsiness)
Skin Pricking (may lead to bleeding or infection)	Risk of choking
Easy Bruising (NAI consideration)	Risk of Pneumonia
Risk of VTE	Transition care