Thesis

DIAGNOSTIC WORKUP AND CARE OF PATIENTS WITH PRADER-WILLI SYNDROME – A RETROSPECTIVE STUDY TO COMPARE AUSTRIA AND FRANCE

submitted by
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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 28.05.2024 *Julia Kraus m.p.*

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Zusammenfassung

Einleitung

Ziel dieser retrospektiven Studie ist es, den aktuellen Status quo der Prader-Willi-Diagnostik und -Therapie in Österreich zu erfassen und diesen mit Daten aus Frankreich zu vergleichen. Als zentrale Fragestellung wurde das Alter bei Diagnosestellung analysiert, zusätzlich wurden Daten zur Schwangerschaft, der Geburt, der Neonatalperiode und den Therapiemaßnahmen, insbesondere in Bezug auf die Einleitung einer Wachstumshormon-Therapie, evaluiert und mit Frankreich verglichen.

Methoden

Die Datenerhebung in Österreich erfolgte an der Universitätsklinik für Kinder- und Jugendheilkunde Graz und der Universitätsklinik für Kinder- und Jugendheilkunde Salzburg. Insgesamt wurden Daten zu 29 Patientinnen und Patienten aus Österreich der Geburtsjahrgänge 2000 bis 2021 erhoben und mit Daten von 60 Kindern aus Frankreich verglichen.

Ergebnisse

Beide Geschlechter waren in unserer Studie gleich stark vertreten (48% männlich, 52% weiblich). Das Prader-Willi-Syndrom wurde in Österreich im Median im Alter von 52 Tagen diagnostiziert. Bei 17/25 Kindern (68%) wurde die Diagnose innerhalb der ersten 90 Lebenstage gestellt, 12% wurden nach dem 3. Lebensjahr diagnostiziert. 28/29 Neugeborene wurden nach der Geburt hospitalisiert, eine Ernährungssonde war bei 16/20 Säuglingen erforderlich. Eine Physiotherapie wurde in 25/27 Fällen (92,6%), eine Ergotherapie in 17/20 Fällen (85%) und eine Logotherapie in 12/18 (67%) Fällen eingeleitet. Zum Zeitpunkt der Datenerhebung erhielten 27/29 Fällen (93,1%) bereits eine Wachstumshormonbehandlung. Diese wurde median im Alter von 2 Jahren begonnen.

In Frankreich wurde das Prader-Willi-Syndrom im Median mit 23 Tagen diagnostiziert und damit statistisch signifikant früher als in Österreich mit Median 52 Tagen ($p<0,001$). Ebenso signifikant kürzer war die Dauer der genetischen Tests ($p<0,001$), hier steht eine Dauer von median 25 Tagen in Österreich 10 Tagen in

Frankreich gegenüber. Die Wachstumshormonbehandlung wurde mit einem Median von 12 Monaten ebenso signifikant früher ($p<0,05$), aber in dieser Studie auch signifikant seltener (40 % der Fälle im Gegensatz zu 93,1 % in Österreich ($p<0,001$)) eingeleitet.

Diskussion

Die Ergebnisse heben den Einsatz von Wachstumshormontherapie und multidisziplinärer Betreuung in Österreich positiv hervor, zeigen aber ebenso Verbesserungspotenzial auf, insbesondere hinsichtlich der Vermeidung von späten Diagnosestellung und dem frühzeitigeren Einsatz von Wachstumshormonen. Die signifikant häufigere Anwendung von Wachstumshormonen in Österreich im Vergleich zu Frankreich sticht besonders heraus, ist allerdings auf die spätere Diagnosestellung und das Studiendesign zurückzuführen und spiegelt sich nicht in anderen Studien wider.

Weitere Studien sind erforderlich, um Gründe für besonders späte Diagnosestellungen zu klären und den Weg für den frühzeitigen Einsatz von Wachstumshormonen zu ebnen, um schlussendlich eine bestmögliche Prognose für Patientinnen und Patienten mit Prader-Willi Syndrom sicher zu stellen.

Abstract

Introduction

The aim of this retrospective study was to analyse the current status of Prader-Willi syndrome diagnosis and treatment in Austria and to compare it with data from France. The central question was the age at diagnosis. Furthermore, data on pregnancy, birth, neonatal period, and therapeutic measures, in particular with regard to the introduction of growth hormone, were evaluated.

Methods

Data collection in Austria took place at the Department of Paediatric and Adolescent Medicine at the University Hospital of Graz and the University Hospital of Salzburg. In total, data from 29 Austrian patients born between 2000 and 2021 was collected and compared with data from 60 children from France.

Results

In Austria, Prader-Willi syndrome was diagnosed at a median age of 52 days. 17/25 children (68%) were diagnosed within the first 90 days of life, 12% were diagnosed after the age of 3 years. 28/29 newborns were hospitalised after birth, and 16/20 infants required a feeding tube. Physiotherapy was started in 25/27 cases (92.6%), occupational therapy in 17/20 cases (85%), and speech therapy in 12/18 cases (66%). At the time of data collection, 27/29 cases (93.1%) were already receiving growth hormone treatment, which was started at a median age of 2 years.

In France, Prader-Willi syndrome was diagnosed at a median age of 23 days, which is statistically significantly earlier than in Austria ($p<0.001$). The duration of genetic testing was also significantly shorter ($p<0.001$), with a median duration of 25 days in Austria compared to 10 days in France. Growth hormone treatment was also initiated significantly earlier with a median of 12 months ($p<0.05$), although less frequently (40% of cases compared to 93.1% in Austria ($p<0.001$)).

Discussion

The results positively highlight the use of growth hormone therapy and multidisciplinary care in Austria. However, there is still room for improvement in

terms of early diagnosis and initiation of growth hormone treatment. The significantly more frequent administration of growth hormone in Austria stands out in particular but can be attributed to the later diagnosis compared to France and the chosen study design. It is not reflected in other studies.

Further research is required to clarify the reasons for late diagnoses and lay the basis for establishing an early start of growth hormone therapy in order to ultimately ensure the best possible prognosis for patients with Prader-Willi syndrome.

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List of abbreviations

PWS	Prader-Willi syndrome
GH	growth hormone
GI	gastrointestinal
IGF	insulin-like growth factor
GERD	gastroesophageal reflux disease
PA	physical activity
SD	standard deviation
UPD	uniparental disomy
DNA	Deoxyribonucleic acid
MS-PCR	Methylation-Specific Polymerase Chain Reaction
MS-MLPA	Methylation-Specific Multiplex Ligation-dependent Probe Amplification
IC	imprinting center
CGH	comparative genomic hybridisation
SNP	single nucleotide polymorphism
IGF-1	insulin like growth factor 1
BSID-II	Bayley Scales of Infant Development II
AIMS	Alberta Infant Motor Scale
GMFM	Gross Motor Function Measure
%FM	percentage of fat mass

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1 Introduction

The present study aims to analyse the current status quo of Prader-Willi patients in Austria and to compare the findings with existing data from France, collected in the course of the study “Early care in achieved but should be improved.” by Bar et al. (1)
The focus here is on the age at diagnosis. However, to provide an accurate and comprehensive overview, several other factors are also being investigated, including genetic factors, early care, and the use of growth hormone therapy.
Nevertheless, before taking a deep dive into those specific settings, a closer look at the theoretic background of Prader-Willi syndrome (PWS) is necessary to understand symptoms, diagnosis, and treatment.

1.1 Background of Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder that involves a broad spectrum of symptoms, among them dysmorphic features, neurologic and cognitive impairments, as well as endocrine, metabolic, and behavioral disturbances. (2)
The reported prevalence in newborns varies between 1:10,000 and 1:30,000, with no difference in gender. (1,3) Even though it is considered a rare disease, the PWS is found to be the most common syndromal cause of life-threatening obesity. (2,4)

1.1.1 Genetic causes

The cause of this genetic disorder is a lack of expression of imprinted genes on the paternally derived chromosome 15, region q11-q13. This region is divided into four parts, the most proximal and distal sections do not contain imprinted genes, whereas the two in between consist of a paternal-only expressed region and a maternal expressed region. Since those regions are active exclusively on the chromosome from one parent and silenced on the other allele, a loss, or the failure to express the, in the case of PWS paternally imprinted, genes will lead to a missing gene product and thus Prader-Willi syndrome. In contrast, a loss of maternally

expressed genes will lead to its sister genomic imprinting syndrome, the Angelman syndrome. (5,6)

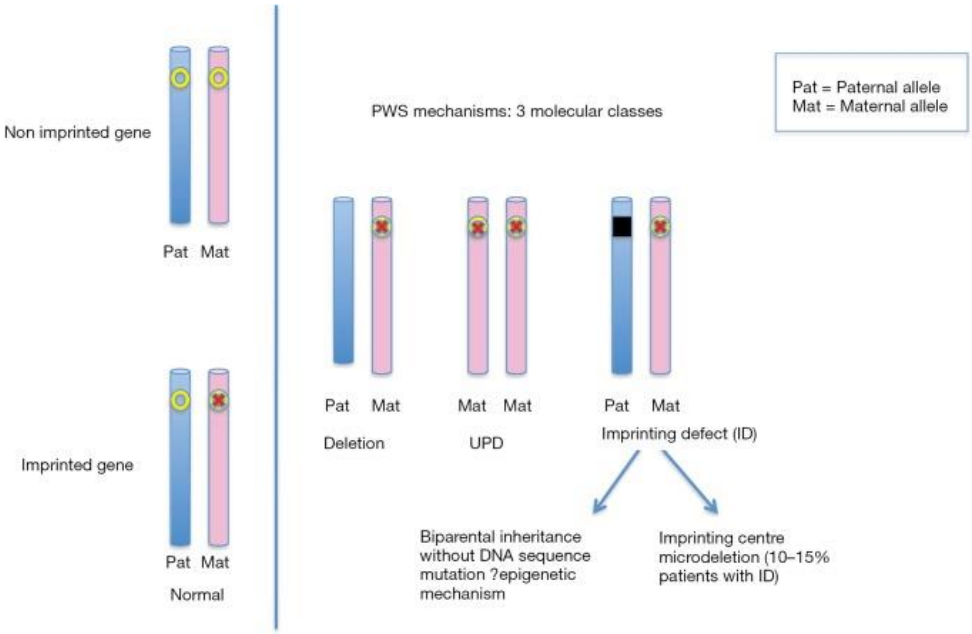

Figure 1 The three molecular classes of PWS.
Shown in this image are the three molecular classes of PWS. Blue represents the paternal Chromosome, pink the maternal. The yellow circle indicates the critical region for PWS. While the open circles indicate an active gene, the red cross stands for an inactive (imprinted) gene. The black box represents an IC defect. Adapted from (7)

There are 3 molecular classes of PWS: A deletion of the PWS critical region, a uniparental disomy (UPD), or an imprinting center (IC) defect. (7)

In most cases of PWS (about 70%), the loss of region q11-q13 in the paternally derived chromosome is due to a de novo deletion. Depending on the size, different deletions can be distinguished, the most common are type 1 and type 2, with the type 1 deletion starting more proximally and therefore resulting in greater gene loss. Approximately 25% of patients with PWS result from maternal uniparental disomy (mUPD) 15, where both chromosomes originate from the mother. Less common causes are genomic imprinting defects due to epimutations or microdeletions of the imprinting center, as well as translocations or rearrangements of chromosome 15. (2,7)

Within the affected region, especially the SNORD116 gene is found to be the possible determinant gene for developing the full spectrum of Prader-Willi syndrome including infantile hypotonia, craniofacial anomalies, intellectual disability, growth

hormone deficiency, hypogonadism, behavioral problems and hyperphagia, leading subsequently to obesity. (2,8)

1.1.2 Diagnostic approach

In 1993 consensus diagnostic criteria based on the clinical presentation have been established by Holm et al. (Table 1). (9)

Major criteria	**Points**
1. Neonatal and infantile central hypotonia with poor suck, gradually improving with age	1
2. Feeding problems in infancy with the need for special feeding techniques and poor weight gain/failure to thrive	1
3. Excessive or rapid weight gain on the weight-for-length chart (excessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention	1
4. Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, down-turned corners of the mouth (3 or more required)	1
5. Hypogonadism—with any of the following, depending on age: a. Genital hypoplasia (male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age [<5th percentile]; female: absence or severe hypoplasia of labia minora and/or clitoris b. Delayed or incomplete gonadal maturation with delayed pubertal signs in the absence of intervention after 16 years of age (male: small gonads, decreased facial and body hair, lack of voice change; female: amenorrhea/oligomenorrhea after 1age 16)	1
6. Global developmental delay in a child younger than 6 years of age; mild to moderate mental retardation or learning problems in older children	1
7. Hyperphagia/food foraging/obsession with food	1
8. Deletion 5q11–13 on high resolution (>650 bands) or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region, including maternal disomy	1
Minor criteria	
1. Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age	0.5
2. Characteristic behavior problems—temper tantrums, violent outbursts and obsessive/compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)	0.5
3. Sleep disturbance or sleep apnea	0.5
4. Short stature for genetic background by age 15 (in the absence of growth hormone intervention)	0.5
5. Hypopigmentation—fair skin and hair compared to family	0.5
6. Small hands (<25th percentile) and/or feet (<10th percentile) for height age	0.5
7. Narrow hands with straight ulnar border	0.5
8. Eye abnormalities (esotropia, myopia)	0.5
9. Thick viscous saliva with crusting at the corners of the mouth	0.5
10. Speech articulation defects	0.5
11. Skin picking	0.5
Supportive findings (Are not scored but increase the certainty of diagnosis)	
1. High pain threshold	-
2. Decreased vomiting	-
3. Temperature instability in infancy or altered temperature sensitivity in older children and adults	-
4. Scoliosis and/or kyphosis	-
5. Early adrenarche	-
6. Osteoporosis	-
7. Unusual skill with jigsaw puzzles	-
8. Normal neuromuscular studies	-

Table 1 Consensus Diagnostic Criteria of Prader-Willi syndrome
Adapted from (9)

The diagnostic criteria are divided into three groups of different value:

1. Major criteria value one point each.
2. Minor criteria value half a point.
3. The supportive findings are not included in the score but enhance the certainty of the results and inform the user about less common and nonspecific features of the syndrome.

A diagnosis requires a total score of 5 points, with at least 4 major criteria, for children 3 years and younger and a score of eight points with a minimum of 5 points from major criteria in everyone above 3 years. (9)

Since the development of those diagnostic criteria in 1993, genetic testing has become more broadly available. The purpose of the diagnostic criteria is therefore no longer primarily to establish a diagnosis per se, but rather to raise diagnostic suspicion, ensure that all appropriate individuals are tested, and avoid unnecessary testing costs. (10)

In a retrospective study by Gunay-Aygun et al., the sensitivity and validity of the diagnostic criteria were investigated and subsequently revised. Their results indicate that most of the published criteria have acceptable sensitivities. Nevertheless, 16.7% of patients with a confirmed molecular diagnosis did not meet the clinical diagnostic criteria, suggesting that these criteria may be too restrictive. (10)

Taking those findings and their experience into account, they suggested testing criteria adapted to age groupings based on the typical phases of PWS:

For children between two and six years, testing should be administered in case of present hypotonia with a history of poor suck and general developmental delay. From six to 12 years of age, the prior criteria apply as well, plus the occurrence of excessive eating with uncontrolled, central obesity.

After the age of 12 years, testing is recommended for patients displaying cognitive impairment, excessive eating with uncontrolled obesity, hypogonadotropic hypogonadism and/or typical behavior problems. (10) An open international multidisciplinary expert meeting in 2006 further discussed recommendations on diagnosis and management and concluded that the presence of hypotonia and poor suck in a newborn is sufficient, to prompt for genetic testing. (11) These recommendations were further substantiated by Grootje et al. and their study on pre- and neonatal characteristics in a cohort of 244 infants with PWS. (12)

Nowadays, genetic testing is ultimately required and necessary to confirm the diagnosis of PWS. Due to the complex underlying genetic mechanisms, a definitive and thorough diagnosis requires at least two different tests. (7)
DNA (Deoxyribonucleic acid) methylation analysis is the preferred diagnostic method, as it detects over 99% of cases, including deletions, maternal uniparental disomy, and imprinting center defects. (13)
There are two common options for DNA methylation analysis: MS-PCR (Methylation-Specific Polymerase Chain Reaction) and MS-MLPA (Methylation-Specific Multiplex Ligation-dependent Probe Amplification). MS-MLPA has an advantage over MS-PCR as it can identify both the DNA methylation status and deletions, making it the first choice for the molecular diagnosis of PWS. If the DNA methylation status shows a hypermethylation with a loss of copy numbers, accordingly a loss of genes, this indicates a paternal deletion. (13) MS-MLPA can also detect microdeletions within SNORD116 and small IC-deletions as well as UPD. However, it cannot distinguish between an UPD and an imprinting center mutation (7) In case of a hypermethylation with a normal copy number, a mUPD, an epimutation, or a Robertsonian translocation could therefore be present.
To distinguish further, a Fluorescence In Situ Hybridization (FISH) or high-resolution karyotype can be performed. If the FISH result is normal, a translocation is eliminated, and DNA polymorphism or linkage analysis then can differentiate mUPD from an epimutation. (13)

The MS-MLPA cannot detect rearrangements without a loss of copy numbers, nor can it detect changes of copy numbers throughout the entire genome. (7) Therefore, if the MS-MLPA result is normal, but PWS nevertheless strongly suspected, DNA sequence analysis can be performed to identify an imprinting center (IC) deletion and pathogenic variants in key genes. (13)

An alternative approach to diagnostic tests would be to begin with a comparative genomic hybridisation (CGH) microarray, as it is capable of detecting deletions, partial maternal UPD (isodisomy), and unbalanced chromosome rearrangements. (7,13) The advantage of this method over MS-MLPA is that the entire genome is visible with the CGH microarray, which enables the detection of genomic changes

outside the critical region for PWS. However, it is unable to distinguish between PWS and Angelman syndrome, nor can it detect balanced chromosome rearrangements or all cases of uniparental heterodisomy UPD, even when paired with a single nucleotide polymorphism (SNP) array. (7,13) Consequently, a microsatellite analysis or a trio-analysis may still be required at a later stage to confirm the diagnosis. (7)

1.1.3 Symptoms of Prader-Willi syndrome – a specific time course

Prader-Willi syndrome presents with a wide range of symptoms, which typically develop in a particular time course.

1.1.3.1 Peri- and neonatal period

Already during pregnancy, reduced fetal activity can be observed in patients with Prader-Willi syndrome. Reduced fetal movements are one of the most frequently noted signs, occurring in around 80% during the pregnancy. (12,14) Concerning the delivery, a higher rate of breech positions and caesarean section, as well as a higher frequency of induction of labor were found in PWS. (12,15) Breech presentation may be favored by fetal hypotonia and the limited movements in the womb, furthermore, inducing the likelihood of a caesarean section. The higher frequency of caesarean sections reflects the generally higher incidence of complications during pregnancy and the perinatal period in PWS patients. (12,14,15) Polyhydramnios, in particular, is significantly more common in PWS, presumably due to reduced fetal swallowing in utero, at least partly caused by muscular hypotonia. (14,16) Other complications such as gestational hypertension/pre-eclampsia, premature rupture of membranes, or fetal heart rate and rhythm disturbances also occur more frequently. (12,14-16)
At birth, both, a lower weight, and length can be noticed in newborns with PWS. Especially the birth weight standard deviation (SD) is found to be significantly lower than in a healthy comparison group. Newborns were also more frequently diagnosed as small for gestational age (SGA). (12)
Regarding the parental age, high maternal age at birth (>35 years) is more frequently found in PWS. (12) Maternal age is the highest in patients with a mUPD,

explainable by the underlying genetic mechanism, where higher maternal age is a known risk factor to disturb meiosis 1 and cause chromosomal abnormalities. (12,17)

During the neonatal period, the main problems are hypotonia and poor sucking, respectively feeding difficulties, which concern almost every patient with PWS. (12,14,15) Especially hypotonia can be observed in outstanding high frequencies. In a study by Grootjen et al. on pre- and neonatal characteristics of children with PWS, every newborn of the 244 investigated presented with hypotonia. (12) Similar results were noted in a multicenter study by Singh et al. and studies by Yang et al. and Çizmecioğlu et al., where hypotonia was noted in at least 98,5% and up to 100%. (14,15,18) Poor sucking and feeding difficulties were reported in 99% of cases and all four studies noted a high rate of tube feeding (69.4%-93.9%). (12,14,15,18)

Besides the omnipresent feeding difficulties, respiratory problems are a common problem. The decreased muscle mass in combination with hypotonia leads to an elevated risk of respiratory distress and asphyxia, especially in case of illnesses. (5) Furthermore, studies indicate that the feeding difficulties themselves, and dysphagia in particular pose a risk to choking and aspiration, which in turn provokes pulmonary infections. (19,20) A retrospective study by Salehi et al. reviewing videofluoroscopic swallow studies in 10 infants with PWS noted aspiration events in 87% and pharyngeal residue in 71%, suggesting that a high rate of swallowing dysfunction may be present in PWS patients. (20)

Birth asphyxiation was noted by Yang et al. in 32.1% of cases (14) and breathing difficulties were reported in 64.4% by Grootjen et al. (12)

Those problems usually require hospitalization after birth, leading to a hospitalization rate of 94.8% in the neonatal period (14) and a median duration of around 20 days. (12,14)

In our reference study by Bar C et al. 93% of the investigated 61 patients had been hospitalized, 75% directly after birth and with a median hospital stay of 32 days. Concerning feeding problems, out of 58 newborns, 84% required a nasogastric tube with a median administration time of 38 days.

Data about respiratory measures was obtained for 49 infants and showed that nasal oxygenotherapy was administered in 33% of cases, continuous positive airway

pressure (CPAP) was necessary in 33% (out of 42 infants in this case) as well and 12% were intubated. (1)
In boys, an outstanding high frequency of Cryptorchidism of around 95% was observed. (12,18)

1.1.3.2 Early childhood

Around the age of two years, the feeding pattern slowly shifts from feeding difficulties and a tendency towards anorexia to excessive weight gain with an insatiable appetite. Hyperphagia is a primary problem in PWS since it affects the vast majority of patients and leads to severe complications like early-onset obesity, as well as its complications and associated diseases like type 2 diabetes, right-side heart failure, or obstructive sleep apnea. (5,21) The exact pathophysiology behind this hyperphagia is still unknown, although hypothalamic dysfunction and disruption in hormonal cycles involved in satiety/appetite control, decreased resting energy expenditure, and changes in body composition are considered responsible. (5,21,22) Infants were also found to have a thyroid hormone deficiency in about 20-30% of cases, leading to an altered metabolic rate and predisposing them to developing obesity. (22)
Besides the hyperphagia, this phase is marked by global developmental delays and behavioral problems, among them temper tantrums, difficulty in changing routines, obsessive-compulsions and manipulatory as well as aggressive behavior.
The characteristic phenotype includes a narrow forehead, short-upturned nose, downturned corners of the mouth and hypopigmentation. Later, small hands and almond-shaped eyes become more prominent, whereas central obesity is a typical finding from early childhood on. (5,21)

1.1.3.3 Adolescence

During adolescence, hypogonadism and infertility occur in most of the PWS patients. Central as well as primary hypogonadism have been reported in different patterns and varying combinations. Puberty is in most cases either absent, delayed, or incomplete. (5,21,23)

While the age of onset of puberty is usually normal in boys, maturation typically stops at an average bone age of 13.5 years, resulting in a reduction in the size of the external genitalia in males, especially the testicles, with an observed average volume of 4ml, but also the penis size. Testosterone levels increase with the onset of puberty but remain relatively low. (5,21,23)
In women, the major labials and clitoris may be hypoplastic. Menstruation can occur, but most PWS patients have secondary amenorrhea or subsequent oligomenorrhea. (5,21) There are a few reported cases of pregnancies in women with PWS, men, however, are considered infertile and no reports on fathering children have been reported so far. (23)

1.1.4 Growth and body weight

Besides abnormalities in sex hormone-mediated functions, growth hormone (GH) deficiency is the most frequently reported endocrinopathy in PWS. A disturbance in the GH-IGF-1 (insulin-like growth factor 1) axis, more precisely a subnormal reserve in GH and IGF-1 generation, is suspected and deficiencies in both hormones are therefore observed. (24,25) The prevalence of GH deficiency in children varies between 40-100% in different studies, depending on the stimulation test used. (26) A more recent study including data from a French database of 142 children found a frequency of 86%. (27)
Those deficiencies lead to a diminished growth response and consequently to a reduced pubertal growth spurt, growth deceleration and altogether a short final height. Without treatment, the average height during adulthood is 155cm for men and around 147cm for women. (5,24,28)

It is not only the small stature that is a result of growth hormone deficiency. Growth hormone deficiency is also associated with poor muscle tone and strength, decreased movements, diminished energy expenditure, and exercise tolerance, as well as an abnormal body composition, characterised by a decreased muscle mass and an increased fat mass. (29) These mechanisms contribute to the development of obesity, which is a significant cause of complications and one of the main symptoms of PWS. (30) Especially amongst adults, a high prevalence of obesity

(82% - 98% depending on the study group) has been reported, whereas the prevalence in children and adolescents is found to be lower, at approximately 40%. However, given the typical course of Prader-Willi syndrome, the prevalence of obesity varies significantly between different age groups. (31)

In addition to growth hormone deficiency, other hormonal disorders such as hypothalamic satiety disorders, disorders of hormonal regulation of food intake and gastrointestinal motility, and low energy expenditure contribute to the development of severe obesity. (22,30)
The reduced energy expenditure is caused by a generally reduced muscle mass and a low level of physical activity. The decreased physical activity results from the a priori decreased muscle tone, and if already present, obesity. This creates a vicious circle in which obesity, in turn, decreases physical activity, which does not build muscle mass, and thus energy expenditure remains low. (30)

1.1.5 Complications and causes of death

These circumstances are particularly unfavorable because obesity-associated complications are among the leading causes of death for PWS patients in adulthood. (32)
In a study by Butler et al., the average age at death was 29.5 +/- 16 years (33), a life expectancy well below that of the healthy population. (34) This study similarly found that respiratory failure was the most common cause of death, especially in infants and children, while deaths due to obesity-related morbidity, cardiovascular disease, pulmonary embolism, and renal failure were especially important in adulthood.
20% of the deaths recorded were in children and young people under the age of 18, with the majority occurring in adulthood, accounting for 70%. Overall, they concluded that more than half of the deaths were due to obesity-related factors. (33)
Similar results were found in a study by Pacoricona Alfaro et al., who identified the causes of death in 104 PWS patients in France. Respiratory causes such as respiratory failure and infections were found to be responsible for more than 50% of deaths. Muscle hypotonia, reduced cough efficiency, abnormal response to hypoxia

or hypercapnia, and silent aspiration were hypothesized as reasons for these respiratory causes. Although the classification of causes of death differs slightly from similar studies and therefore limits comparisons, cardiac and vascular causes were found to be the third most common cause of death after respiratory causes and sudden death. (35)

A study by Proffitt et al. compared data collected from 114 deceased and 1915 living people with PWS to assess factors contributing to mortality. The comparison showed that obesity and obesity-related health problems such as diabetes, respiratory complications, sleep apnea, and heart problems were more common in the deceased population. Individuals in the living group also tended to be diagnosed earlier than those in the deceased population (3.8 years versus 7.4 years), although not statistically significant, and were more likely to undergo growth hormone therapy (51.3% versus 21.9%). (32) It should be noted that much of the data had already been evaluated during the study by Butler et al. (33)

Apart from obesity and obesity-related causes of death, there are various other common comorbidities of PWS patients.

Pemmasani and Yandrapalli surveyed those comorbidities in a total of 480 patients and evaluated their frequency (shown in Table 2).

Comorbidity N (%)	Total sample N = 480 (%)	Ages 0–12 N = 132 (%)	Ages 13–25 N = 108 (%)	Ages 26–39 N = 112 (%)	Ages 40 and above N = 128 (%)
Female sex	238 (50)	65 (49)	49 (45)	61 (55)	63 (49)
Dyslipidemia	71 (15)	0	14 (13)	29 (26)	28 (22)
Obesity	197 (41)	17 (13)	54 (50)	72 (64)	54 (42)
Diabetes mellitus	122(25)	<10	27 (25)	45 (40)	46 (36)
Anemia	60 (13)	<10	13 (12)	12 (11)	31 (24)
Hypothyroidism	77 (16)	8 (6)	16 (15)	24 (21)	29 (23)
Hypertension	132 (28)	3 (2.3)	28 (26)	42 (38)	59 (46)
Chronic lung disease	71 (15)	19 (14)	17 (16)	15 (13)	20 (16)
Obstructive sleep apnea	127 (27)	36 (27)	35 (32)	30 (27)	26 (20)
Venous thromboembolism	22 (5)	<10	<10	<10	13 (10)
Coronary artery disease	14 (3)	<10	<10	<10	<10
Congestive heart failure	44 (9)	0	10 (9)	12 (11)	21 (16)
Chronic kidney failure	31 (7)	<10	<10	<10	14 (11)
Depression	31 (7)	0	<10	13 (12)	14 (11)
Mood disorders	75 (16)	0	17 (16)	29 (26)	28 (22)
Anxiety	44 (9)	<10	12 (11)	18 (16)	12 (9)
Psychoses	33 (7)	0	<10	10 (9)	17 (13)

Table 2 Age-stratified prevalence of selected comorbidities in hospitalized individuals with Prader–Willi syndrome
Adapted from (36)

Obesity was, with an overall prevalence of 41%, the most frequently observed. It was especially common in the age group from 26 to 39 years, almost two third of the PWS patients in this age group were obese.

The second most frequent comorbidity was found to be hypertension, with a prevalence of 28% in the total sample. With increasing age, the frequency rose continuously.

Almost equally often, PWS patients suffer from obstructive sleep apnea, with a prevalence of 27%. Diabetes mellitus Type 2 was found in one quarter of all patients. Mood disorders, Hypothyroidism, Dyslipidemia, and chronic lung disease all occurred with a frequency of about 15%. Slightly less frequent were anemia at 13%, congestive heart failure and anxiety at 9%, and psychoses, depression, and chronic kidney failure at 7%. The least frequent comorbidities were venous

thromboembolism at 5% and coronary artery disease at 3%, with a prevalence of thromboembolism of 10% in the age group over 40 years. (36)
A study by Butler, Oyetunji and Manzardo shows that this prevalence of thromboembolism still exceeds the prevalence found in a comparable population without PWS. They observed that across all age groups studied, deep vein thrombosis and pulmonary embolism were 2.55 times more likely in people with PWS than in obese controls. (37)
Another common comorbidity that has not been considered in the studies mentioned so far is Scoliosis. Spinal deformities, especially Scoliosis, are commonly found in PWS patients with a lifetime risk of approximately 70%. (38) Prevalences vary in different age groups and several studies suggest two age peaks of scoliosis development, one before the age of 4 and one near adolescence. (38-41) Odent et al. found that 43% of individuals with Prader-Willi syndrome had scoliosis, with the rate increasing to 68% in those who reached skeletal maturity. (39) Nagai et al. observed scoliosis in 22% of patients aged 5 years or younger, 25% in those aged 6-11 years, and 68% in those over 12 years old. (40)De Lind van Wijngaarden et al. reported similar results with a scoliosis prevalence of 23% in infants, 29% in juveniles, and 80% in adolescents. (41)
Furthermore, Odent et al. found in their study that higher BMI was associated with the development of a kyphotic deformity, which likewise is associated with the need for surgery. (39)

Prader-Willi syndrome furthermore predisposes individuals to osteoporosis due to hypogonadism and growth hormone deficiency, exacerbated by factors like low physical activity and inadequate vitamin D levels. (8,42) There is also an association between PWS and right-sided heart failure, fatty liver, ulcers, and cellulitis, as well as gastrointestinal issues like dysmotility and electrolyte imbalances. The electrolyte imbalances can result from excessive fluid intake, low vasopressor levels, or the use of certain medications like antidepressants or diuretics. (8) Gastrointestinal dysmotility leads to difficulties in swallowing, choking risks, and issues like gastroesophageal reflux disease (GERD) and silent aspiration. Factors like delayed gastric emptying contribute to gastroparesis and constipation. A high pain threshold and lack of the typical vomiting response to abdominal discomfort can further complicate the detection of gastrointestinal problems. (8)

1.1.6 Treatment approaches

To ensure an individually adapted treatment, a multimodal approach should be chosen, and a multidisciplinary team, including at least a paediatric endocrinologist, a psychologist, a neurologist/neuropsychiatrist, and a dietician, is necessary.(43)

The current management of PWS consists of three main therapeutic measures: (44,45)

1. Dietary management
2. Physical activity
3. Pharmacological therapies, mainly GH replacement. (44,45)

1.1.6.1 Dietary management

Especially dietary management remains a key point in the treatment approaches since it counteracts hyperphagia, a major reason for the development of obesity and a remaining problem in the therapeutic approach. Even though new studies have revealed several potential molecular targets, the development of a pharmaceutical therapy remains complicated due to a limited understanding of the pathogenesis. (31,44)

Therefore, the fundamental measures to counteract hyperphagia and prevent obesity remain dietary management, like restricted food access, special diets, and physical activity. A strict control is necessary, because with the onset of hyperphagia, a constant focus on food establishes, which is challenging to redirect. Patients with PWS are therefore still struggling to live an independent life, because of the need for significant environmental restrictions and food supervision. This focus on food has a negative impact on the quality of life, education, job performance, and personal relationships. Unfortunately, with an inadequate diet, those struggles can even be increased, as an extreme restriction in caloric intake further promotes the hunger drive and behavioural problems. (31,44)

Considering the administered diet, further research is needed to determine its optimal composition. As far as recent studies show, a well-balanced, but energy-restricted diet that is rather high in dietary fiber is advised most often. (31,44,46)

In a study by Miller et al., the dietary management of two groups of PWS patients was compared over a period of 5 to 7 years. While both groups were administered a diet with energy restriction, one group had a specific table of macronutrient distribution to follow. Of the total 63 participating children with PWS, a group of 33 patients adhered to a diet consisting of 30% fat, 45% carbohydrates, and 25% protein, with a mandatory intake of at least 20g fibers per day. This group was found to have better weight management (body mass index 0.3 SD versus 2.23 SD), significant improvements in body fat (19.8% versus 41.9%), and a lower respiratory quotient, thus a better energy expenditure in comparison to the group without a specific macronutrient distribution in addition to the energy restriction. (46)

1.1.6.2 Physical activity

Additional to an adequate dietary regimen is physical activity. As already mentioned, PWS patients have a lower energy expenditure than the healthy population and engage in less physical activity, even when compared to individuals with similar BMI. They furthermore show decreased exercise tolerance and stamina, reduced cardiorespiratory capacity, and diminished hormonal responses to physical stress. (31,44)

In a review of Observational and Interventional Studies on physical activity in PWS patients by Bellicha et al., the summary of 14 studies showed, that the total amount of physical activity (PA) is lower in PWS patients than in people with non-syndromic obesity. PWS patients are found to spend more time sitting and engage less, even in light physical activity. Only 5% to 8% of PWS children and only 15-25% of adults with PWS achieve the recommended amount of PA by the WHO guidelines. (47)

Furthermore, the same review evaluated the outcome of different PA interventions in patients with PWS. The most consistent finding was the positive impact of the interventions on physical fitness. This was reflected in better walking ability, higher muscle strength, and better gait parameters. (47) Significant weight loss, on the other hand, was found in only one study, in which several hours of daily exercise were accompanied by a dietary intervention. An observed effect of PA intervention studies on lean body mass and bone mineral density is particularly positive, as these two values are known to be low in PWS patients. (47)

A similar review by Morales et al. investigated the short- and long-term effects of physical training and concluded that: “participation in exercise interventions leads to improvements in PA levels, physical capacity (cardiorespiratory fitness and muscle strength), motor proficiency (body co-ordination and strength and agility) and biochemical profile (glycaemia, lipid profile and inflammation markers), and potential decreases in body mass in this patient population.” (48)

Most of the included studies in this review also noted a positive effect of physical exercise on BMI or total body weight, as well as a beneficial effect at the hormonal level. In the general population exercise poses a stimulus for growth hormone secretion and even though this response is not found in children with PWS, it still stimulates an increase in IGF-1 concentration. A combination of physical exercise and GH treatment could therefore lead to a cumulative effect and have an especially positive impact on general and motor development. (48) One can also speculate that there is a positive effect on height growth.

Miller and Tan concluded in their study, that the first measure to control weight in adolescent patients with PWS should be to increase movement and physical exercise with the aim to increase their muscle strength and consequently their energy expenditure in addition to all the other positive effects above. (31)

1.1.6.3 Growth hormone treatment

As already outlined in Chapter 1.1.4 on growth and body weight, most, if not all children with PWS are considered GH deficient. (49) The resulting problems from this deficiency include reduced growth, but also an altered body composition, low energy expenditure, and reduced muscle strength. (25)

To directly counteract at this point and increase the final height as well as diminish those other disorders, treatment with hGH is generally recommended. (50,51)

1.1.6.3.1.1 Effects on growth, body composition and motor development

Different studies show that GH treatment normalizes linear growth, improves body composition, more precisely lowers fat mass and BMI while lean muscle mass increases. (44,50-54) A systematic review and meta-analysis by Passone et al. including 16 completed randomized controlled trials (RCT) and 20 non-randomized-controlled trials (NRCT) underlines those positive effects. They noted an increase

of +1.67 SD in height, a decrease of 6.5% to 7.0% in fat mass, and of -0.67 SDS in body mass index z-score in the treated group. (54)

It additionally complements the beforementioned physical activity since motor benefits by physical exercise and development of motor skills are enhanced by the GH treatment. (52,55)

In a two-year longitudinal study involving 22 PWS infants with a mean age of 12.9 months, Reus et al. compared two cohorts: one receiving GH immediately after diagnosis and the other initiating GH treatment after a six-month waiting period, with both groups undergoing intense standardized physical training from the outset. (55) The results showed that GH treatment led to earlier achievement of motor milestones, such as independent walking, and increased the overall rate of motor development, as evidenced by improvements in scores on motor development tests such as the Alberta Infant Motor Scale (AIMS) and the Gross Motor Function Measure (GMFM). Infants who received GH at a younger age walked earlier ($p < 0.05$, $r = 0.56$), reached the end of the AIMS test earlier than those who started treatment later, with a significant correlation observed ($p < 0.01$, $r = 0.71$), and had a higher maximum GMFM score, indicating better motor skill attainment, compared to those who started treatment at an older age. (55)

However, in this study, GH treatment did not have a significant effect on the motor scale of the Bayley Scales of Infant Development II (BSID-II), a test that takes fine and gross motor skills into account, and despite all the positive effects observed, a major delay in motor development ultimately persisted. (55)

1.1.6.3.1.2 Effects on cognitive functions and mental development

The positive effects of GH treatment are not only limited to growth and physical benefits. In a study by Butler MG et al. patients with PWS under GH therapy were found to even have significantly higher IQ scores in the Vocabulary section of the Stanford–Binet test in comparison with the non-GH-treatment group (average of 44 versus 38 points). (56) Several other studies also reported benefits of a long-term GH treatment concerning IQ, social skills, cognitive development, and health-related quality of life. (52) Regarding behavioural problems, studies so far do not support that GH treatment leads to significant improvements, although it also does not cause any deterioration with long-term treatment. (57)

Festen et al. and Donze et al. found that mental and motor development significantly improved with GH treatment. (58,59) Donze et al. furthermore noted in their study investigating a group of 63 infants and toddlers, that not only psychomotor development increased and subsequently the disparity between healthy individuals and children with PWS decreased, but also that a younger age at the start of GH treatment resulted in a greater increase in psychomotor development. Psychomotor development was measured using the Bayley Scales of Infant Development II, a test that assesses mental and motor development and considers memory, visual and auditory information processing, eye-hand coordination, imitation, language development, and problem solving, as well as fine and gross motor skills. (59)

1.1.6.3.1.3 Recommendations

As part of the current standard of care for PWS, it is recommended that children with PWS start GH therapy as soon as possible after genetic confirmation of the diagnosis of PWS. (44) The Clinical Care Guidelines of recombinant human GH Therapy, a consensus on recommendations formulated by 43 international experts after an extensive literature review, state that “GH stimulation testing should not be required as part of the therapeutic decision-making process in infants and children with PWS”. (25) However, they recommend an expert multidisciplinary evaluation in addition to the evident genetically confirmed diagnosis, prior to the initiation of a GH treatment. This evaluation should include: (25)

1. A genetic evaluation and counseling, including DNA studies to confirm PWS.
2. An endocrine examination to assess anthropomorphic status, pubertal status, bone age, hypothyroidism or other additional endocrine deficiencies, IGF-I level, and GH response to provocative testing.
3. An assessment of metabolic status, cardiovascular risk profile, and hepatic steatosis.
4. A Body composition evaluation, if available.
5. Referral to a dietician for nutritional evaluation and advice.
6. Assessment of developmental, cognitive, and motor function, with appropriate referrals for psychomotor testing, physiotherapy and occupational therapy.
7. A sleep oximetry and preferably a polysomnographic evaluation in addition

8. Referral to an ear nose and throat specialist in case of enlarged tonsils and adenoids, snoring, or sleep-disordered breathing.
9. A Spine x-ray to evaluate for scoliosis.
10. The instruction of the family on GH treatment, including benefits, risks, and the importance of careful monitoring.
11. The procurement of legal guardian consent and patient assent/consent (25)

The recommended starting dose of GH for infants and children is 0.5mg/m2 per day, which should subsequently be increased to a daily dose of 1.0 mg/m2 (~0.035 mg/kg/day).
GH therapy may be initiated despite the presence of scoliosis or cognitive impairment, but severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, or active psychosis are exclusion criteria. (25)

1.1.7 Benefits of early diagnosis and treatment

Although it is evidently important to offer treatment to patients with PWS, there have also been studies showing that an early administration of GH is especially beneficial. (53,60-62)
Ayet-Roger et al. compared two groups of PWS patients, one who received treatment before 2 years of age and one after. The results are significantly in favor of the group who received GH earlier. The patients had higher scores at the Total Intelligence Quotient, General Ability Index, and general global cognition, implying better adaptive and cognitive performance for this group. (60)
In a prospective study by L.N. Grootjen et al. on the long-term effects of GH treatment, 82 GH-treated children were compared with each other, depending on their age at initiation of GH treatment and with age-matched untreated controls with PWS. The treated children were divided into subgroups according to their age at initiation of GH treatment. A distinction was made between those who started treatment within the first year of life (subgroup A), between one and two years (subgroup B), and between 2-5 years of age (subgroup C). (53) During the study, a significantly lower trend in the percentage of fat mass (%FM) was observed in children who started GH treatment in the first year of life. This was mainly attributed

to a greater decrease in %FM in the first year of treatment in subgroup A, while the decrease was less pronounced in those who started between 2 and 5 years of age. Subgroup A also had a more favorable ratio of trunk to peripheral fat and a lower, although not statistically significant, %FM after 8 years of GH.

Starting GH treatment in the first year of life was also associated with a significantly higher overall IQ (78.1 in subgroup A versus 64.8 in subgroup C). after 8 years of treatment. (53)

Magill et al. observed in their longitudinal retrospective study, that an earlier treatment start has a beneficial effect on height-SDS and metabolic parameters such as low-density cholesterol and fasting glucose. However, they found no notable effect on BMI, lean body mass, or body fat. (62) This may be due to the body composition analysis, performed by bioimpedance spectroscopy instead of a DXA-scan, or due to the lower GH dose of 0.0263-0.0289 mg/kg/day compared to 1 mg/m2/day (~0.035 mg/kg/day) administered. (53,62)

Kimonis et al. also concluded that early diagnosis is important for PWS patients in order to receive specific treatment, such as GH treatment and nutritional counseling, at an early stage and to improve their quality of life. Their study of 352 PWS patients in the United States focuses on the weight trajectory of patients depending on when they were diagnosed with PWS. The results show that patients who were diagnosed early gained weight at or above the 85th percentile much later. For patients diagnosed at less than one year, the estimated median age of weight gain was 10 years, compared to 4 years for patients diagnosed after 3 years. (63)

The study by Proffitt et al. also highlights the importance of early diagnosis. Comparing data from 114 deceased and 1915 living people with PWS, they found that, although not statistically significant, individuals in the living group were diagnosed earlier than those in the deceased population (3.8 years versus 7.4 years) and were more likely to receive growth hormone therapy (51.3% versus 21.9%), supporting the hypothesis that GH treatment may reduce mortality. (32)

1.2 Age at diagnosis

The studies mentioned above in chapter 1.1.7 raise awareness for the necessity of an early diagnosis and initiation of treatment, which inevitably brings up the question about the current age at diagnosis in Austria.

In comparable studies, the age at diagnosis varies widely. (1,3,63-65)

Kim and Cheon, who analysed diagnosis of patients with PWS in Korea, noted a mean age at diagnosis of 13.7 months (2-47 months of age). (64)

In a large study analysing data from 352 people in the United States by Kimonis et al., the median age at diagnosis was 4 months. 37% of these patients were diagnosed after the age of one year and 25% after three years. (63)

Vogels et al. conducted a study on the prevalence, birth incidence, and causes of death in patients with PWS in Flanders, Belgium. The study found that patients under 20 years of age had a median age at diagnosis of 26 weeks (approximately 6 months), with a range from 1 week to 8 years. Patients aged 20 years and older had a significantly later median age at diagnosis of 10 years, with a range from 1 week to 52 years. (65), suggesting that PWS is now generally diagnosed earlier.

Lionti et al. also found a significant difference in the age at diagnosis depending on the year of birth. Of the 132 individuals with a molecularly confirmed PWS diagnosis, those born between 1993 and 2002 had a mean age of 66.5 weeks (~1.3 years) at diagnosis, while those born between 2003 and 2012 were diagnosed at an average of 8.6 weeks, thus approximately 2 months. (66)

When birth prevalence in Australia was investigated by Smith et al., 42 out of 94 investigated patients with confirmed PWS were diagnosed under the age of 15 years, 30 of those were still infants. The median age of those infants was 1 month (ranging from 0.51 to 4.98 months). (3)

1.3 Reference publication

In terms of early diagnosis, the study by Bar et al. stands out with a median age at diagnosis of 18 days. For this study, a team from the French PWS Reference Center collected and analysed data from 61 infants to investigate primarily the birth incidence and secondarily the care of infants diagnosed early in life. Of these 61

infants with molecularly confirmed PWS born in France, 38 were born in 2013 and 23 in 2012. The median age at diagnosis of all PWS patients born in 2012 was 23 days, and in 2013, the aforementioned 18 days. The birth incidence was only calculated for the year 2013 and was 1/20,778 births. Overall, 90% of infants in France are diagnosed within the first two months of life.
According to the authors, in the 5 patients who were diagnosed after the age of 3 months, the delay of the diagnosis was either due to a false negative result in the first genetic test, in this case mostly FISH, or because PWS was not suspected in neonatology in the first place. (1)

The data collected during the reference study in France is used as a comparison for the Austrian data collected in Graz and Salzburg for this thesis.

1.4 Aim of the study

The present study primarily aims to display the current status quo of Prader-Willi patients in Austria and subsequently compare it to France.
To evaluate this status quo adequately, the central question of this study is the age at diagnosis in Austria and how it potentially differs from France, a nation where the diagnosis of PWS and initiation of care starts astonishingly early.
In addition, this study will evaluate various parameters related to early care and treatment, focusing on the initiation of growth hormone treatment and supportive measures such as tube feeding, oxygen therapy, physiotherapy, occupational therapy, and speech therapy.
To address the aim of this study and answer the main research question, a retrospective observational data analysis has been chosen. This study design was selected to maximise the use of available data, enabling the inclusion of patients diagnosed over several years. This provides a larger cohort and a more robust basis for statistical comparison with France.

France has been selected for comparison with Austria primarily because of the exceptional early diagnosis of PWS, as explained above in Chapter 1.3. The PWS Reference Center in Toulouse has extensive experience in managing Prader-Willi

syndrome and has significantly contributed to research in this field. (25,67) The data previously collected in the course of the reference publication aligned with the research questions concerning this present study and was kindly provided by the team of the French PWS Reference Center.

To the best of our knowledge, this is the first study to investigate Prader-Willi syndrome to this extent in Austria and to assess the age at diagnosis.

1.5 Limitations and distinctions

The limitations of this study are mainly related to the nature of the available data and the small number of cases in Austria. As there are fewer cases of Prader-Willi syndrome in Austria than in France, due to the much smaller population, the time span of the study had to be extended in order to obtain a decently sized sample.
Whereas in France, all cases investigated were born between 2012 and 2013, we had to include all available data from a much wider time interval (birth years 2000 until 2021) and therefore also assess patients who were born a lot earlier.
Since the diagnosis of PWS has improved over the years, it is possible that more recent diagnoses are made earlier than before, and studying such a wide timespan affects the results. A child with PWS who was born in recent years may not have received a diagnosis at the time of data collection, which may lead to an underestimation of the age at diagnosis in this particular young age group.
As an Austrian-wide database or registry of all PWS patients has not been established so far and data has only been collected in Graz and Salzburg, it is possible that other regions within Austria are underrepresented. Therefore, results may vary across the country.

2 Material and methods

2.1 Data collection in France

The data collection in France was already conducted in the course of the study "Early diagnosis and care is achieved but should be improved in infants with Prader-Willi syndrome" by the French PWS Reference Centre in association with the Neonatology Unit of the Children's Hospital of Toulouse. Included were children with a molecularly confirmed PWS born in France between January 1st 2012 and December the 31st 2013, laying the focus on 2013 to maximize the dataset for that year. This is the reason, why the birth incidence was only calculated for 2013 and data on infant care was analysed for both years. (1)

To collect the necessary data, the French research team contacted Neonatology units and PWS competence centres through the French Neonatology Society and the French Paediatric Endocrinology and Diabetology Society. In addition, Bar C. et al. obtained data from the French Prader-Willi Association and contacted all cytogenetic and molecular biology laboratories in France where analyses about PWS are conducted to obtain a comprehensive dataset for the years 2012/2013. In order to investigate early care and obtain all relevant parameters, paediatricians were asked to complete a clinical report form to gather information on the family, pregnancy, neonatal phase, diagnosis, and initial care. (1)

2.2 Data collection in Austria

Data on Austrian patients with PWS was collected at the Department of Paediatric and Adolescent Medicine at the University Hospital Graz and the University Hospital Salzburg. Due to the low birth prevalence of PWS (approximately 1:20,000) and the lack of a national registry for PWS patients in Austria, data collection in Graz alone would not have been sufficient. To ensure an adequate sample size, data collection was extended to include the University Hospital of Salzburg, which serves as the Austria-wide reference centre for PWS and has a larger number of patients.
In general, documentation is primarily done on paper, which I investigated directly during this study. According to the staff at the study centres, all known patients

undergoing treatment at that time were present, although it cannot be completely ruled out that the records were incomplete. The paper forms were thoroughly reviewed, and the data was transferred to an Excel sheet, anonymised by means of numbers.

The analysis primarily focused on the age at diagnosis, while also evaluating secondary parameters such as early care and treatment initiation, epidemiological factors, and pregnancy data. Specifically, the study examined parental age, the week of gestation, genetic test results, birth weight, -height and head diameter, postnatal hospitalization, GH treatment, and additional measures including nasogastric tube, oxygen therapy, ventilation, and physio-, speech-, and occupational therapy. A complete list of all investigated parameters is displayed in chapter 2.4.

Although the documentation was not influenced by this study and the focus therefore did not lay on those specific parameters, the data from the Department of Paediatric and Adolescent Medicine at the University Hospital Graz was mostly complete. However, since the Department of Paediatric and Adolescent Medicine at the University Hospital Salzburg acts as a specialized reference centre, and the main caregiving institutions are peripheral clinics, specific data about the neonatal period was significantly more difficult to obtain. Patients are typically monitored by their paediatrician or paediatric endocrinologist at home and attend the reference centre annually to assess progress and coordinate ongoing care.

2.3 Study population

Data was obtained from a total of 90 patients. One patient from Austria was excluded due to Prader-Willi-like syndrome, leaving 29 patients in Austria and 60 in France whose data were processed during this study.

The Austrian data pool consisted of all genetically confirmed PWS patients aged 0-23 years who were followed by the Department of Paediatric and Adolescent Medicine at the University Hospital Graz and Salzburg between 2010 and 2021.

Except for one patient, who was born and diagnosed in Romania, every PWS patient was born in Austria.

2.4 Investigated parameters

The data was first collected in an Excel sheet and then transferred to SPSS to analyse.

The collected parameters are displayed and described in the following Table 3.

Variable	Description
Sex	Female/male
Birthday	dd-mm-yyyy
Country	France/Austria
Region	Region where child is from
Neonatology Department	Hospital where neonate was admitted
Birthplace	City where child was born
Age mother at birth of PWS individual	In years
Age father at birth of PWS individual	In years
Gestational age	Rounded down to the next full week
Diagnostic before birth	Yes/no
Hydramnios	Yes/no
Amniocentesis	Yes/no
Reason Amniocentesis	Why was the amniocentesis done
Result of the Amniocentesis	
APGAR score	After 1 and 5 minutes; As data collection in France did not include an APGAR score after 10 minutes, we also did not obtain this information.
Type of delivery	Vaginal/Caesarean
Weight at birth	In gram
Weight SD	Calculated using an online calculator based on data from Fenton, T.R. and Kim, J.H. (68)
Length at birth	In cm

Length SD	Calculated using an online calculator based on data from Fenton, T.R. and Kim, J.H. (68)
Small for gestational age (SGA)	Yes /no, an individual was considered SGA, if the SD was greater than -2
Head diameter (HD) at birth	In cm
HD SD	Calculated using an online calculator based on data from Fenton, T.R. and Kim, J.H. (68)
Date sampling for genetic testing	dd-mm-yyyy
Date result of genetic testing	dd-mm-yyyy
Age at diagnosis	Calculated in days from the birthday to the date of the genetic test result. If the date of the result was not provided, but documentation stated a diagnosis with for example 2 months, a month was considered to have 30 days and the child was considered to be diagnosed precisely at those two months.
Genetic subtype	UPD, Deletion, IC-defect, and Methylation profile change when PWS was confirmed but the exact genetic type was not specified.
Hospitalization as a newborn	Yes/no
Age at hospitalization	When newborn was hospitalised shortly, but not directly after birth
Duration of hospitalization	In days
Continuous positive airway pressure (CPAP)	Yes/no
Oxygen administered	Yes/no and how long
Tube feeding	Yes/no and how long
Speech therapy	Yes/no
Physiotherapy	Yes/no

Occupational therapy	Yes/no It should be noted that the French reference publication did not evaluate the initiation of occupational therapy, but psychomotor therapy. Nevertheless, it can be reasonably assumed that the two areas of activity overlap considerably.
GH treatment	Yes/no
Age at the start of GH treatment	In months

Table 3 Investigated parameters

2.5 Statistical analysis

The statistical analysis was done using the program IBM SPSS Statistics 28.
To display the current status quo of PWS patients in Austria, the collected data will be displayed in the form of tables and graphs showing, demographics, the age at diagnosis, delay of genetic tests, frequencies of the genetic subtypes, pre- and perinatal factors, neonatal measures, and growth hormone administration.

To statistically assess differences in age at diagnosis between Austria and France, a Mann-Whitney U-test is used after checking the given statistical requirements. This test is also employed to compare metric variables between the two groups, such as the duration of genetic testing or the age at growth hormone administration. Conversely, if the statistical requirements are met, a t-test for independent samples is used to compare the groups.
A chi-square test is employed to assess and compare the frequency distributions of categorical variables, such as the frequency of growth hormone use, initiation of physiotherapy, speech therapy, or the use of a feeding tube between Austria and France.
Any conclusions drawn from the results will be discussed with care, taking into account the limitations and potential biases of the data analysis process.

2.6 Ethics

This study has been approved by the ethics committee of Graz (Ethics approval number: 34-215 ex 21/22) and the ethics committee of Salzburg (Ethics approval number: 1135/2022).

3 Results

3.1 Status quo in Austria

3.1.1 Demographics

The study population in Austria comprises a total of 29 patients, 5 of whom are being followed at the University Hospital of Graz and 24 in Salzburg.

All PWS patients, except for one who was born and diagnosed in Romania, were born in Austria.

Every Austrian region except Burgenland is represented, 7 patients are originally from Upper Austria, 6 from Styria, 5 from Lower Austria, 3 from Salzburg, 2 each from Tyrol and Vienna, and one from Vorarlberg, Carinthia, and Romania. The home region of one child could not be determined.

The distribution of birthdays is relatively even throughout the years, as shown in Figure 2. The earliest recorded birthday was in October 2001, and the latest was in November 2021. It is important to note that since not every patient in Austria was examined during this period, no statement can be made about the birth incidence of PWS.

Both genders are equally represented in this study, as shown in Table 4.

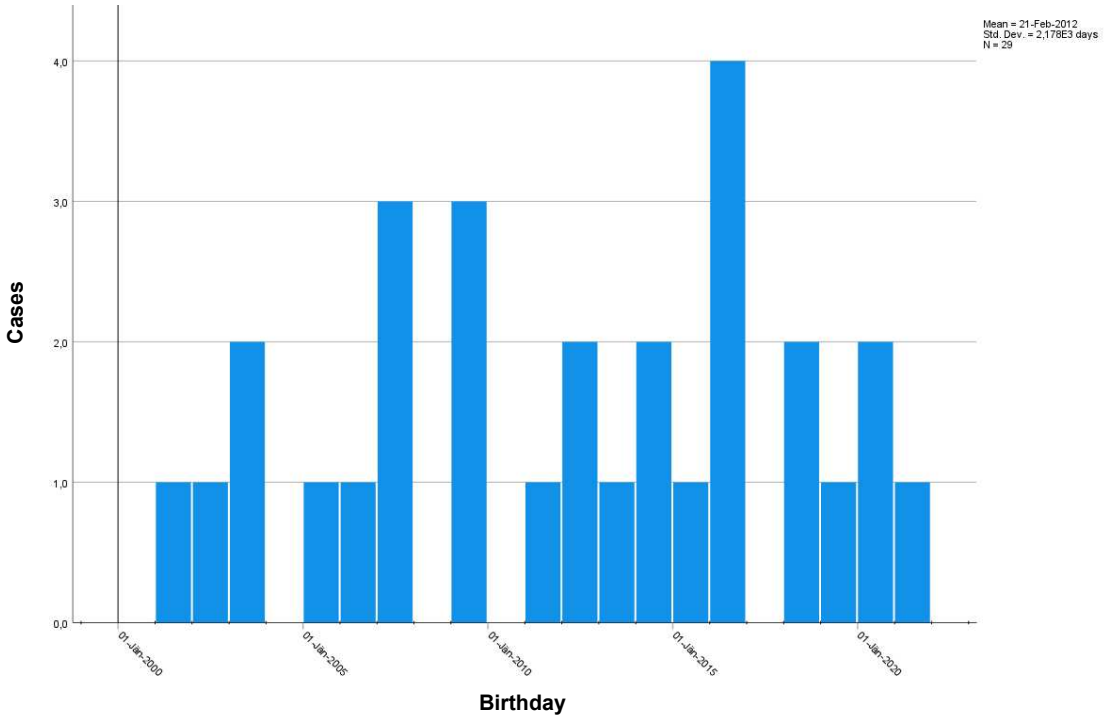

Figure 2 Birthdays of included cases in Austria

		Country			
		Austria		France	
		Count	Column N %	Count	Column N %
Sex	total	29	100,0%	60	100,0%
	male	14	48,3%	28	46,7%
	female	15	51,7%	32	53,3%

Table 4 Gender distribution

3.1.2 Age at diagnosis

The age at diagnosis was evaluated in 25 out of 29 cases, with a median of 52 days in Austria (Table 5). The earliest diagnosis was made at 7 days, while the latest was at 5062 days, which is almost 14 years.

Of the 25 infants evaluated, 17 (68%) were diagnosed before 90 days, or approximately 3 months of age (as shown in Figure 3), and 20/25 (80%) within the first year of life. Five out of 25 infants (20%) were diagnosed after 1 year, and three of them (12%) were diagnosed after 3 years of age.

There was no significant difference in the age at diagnosis between patients born before and after 2013.

	Count	Missing	Mean	Median	Minimum	Maximum	Percentile 75	SD
Age at diagnosis (d)	29	4	427	52	7	5062	205	1066

Table 5 Age at diagnosis in Austria

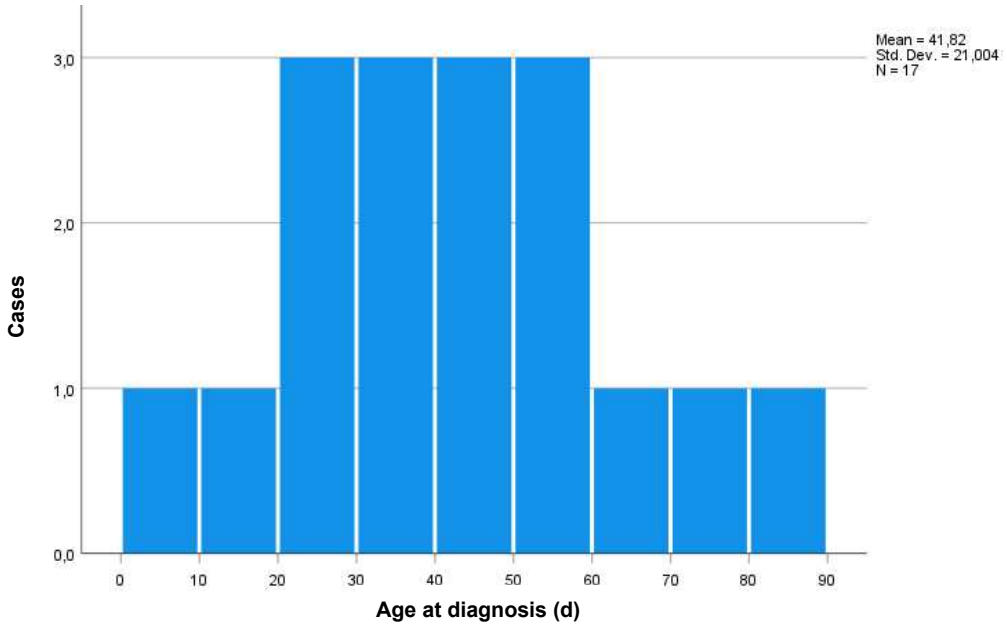

Figure 3 Age at molecular diagnosis of patients diagnosed before 90 days of life (n=17)

The delay of the diagnosis varied widely and was between 6 days and 224 days with a median of 25 days (Table 6). In two cases the genetic analysis took more than six months. The reason for the delay in those two cases has not been explored. In all five cases where diagnosis occurred after the age of one year, genetic analysis was completed within the expected timeframe.

	Count	Missing	Mean	Median	Minimum	Maximum	SD
Delay results (d)	29	8	46	25	6	224	58

Table 6 Delay of genetic results

3.1.3 Genetic subtypes

The genetic subtype was available for 27/29 infants. One patient examined had an abnormal methylation profile, which confirmed the diagnosis of PWS, but without further specification. In a second case, the genetic subtype was narrowed down to either a UPD or an IC defect.

The most frequently observed genetic subtype is Deletion with 58,6% and therefore 17/29 cases (Table 7). One deletion was due to an unbalanced translocation between Chromosome 15 and 19. A UPD was seen in 31% and an Imprinting centre defect occurred in 3,4%, thus 1/29 of cases.

		Count	Column N %
Genetic type	UPD	9	31,0%
	Deletion	17	58,6%
	UPD or IC	1	3,4%
	Imprinting center	1	3,4%
	Abnormal methylation profile	1	3,4%

Table 7 Genetic subtypes

3.1.4 Pre- and perinatal factors

Parental age

Mean maternal age at birth was reported in 21/29 cases and was 33 years, as shown in

Table 8. The mean paternal age was 37 years. Maternal age was significantly higher in infants with UPD in comparison to children with deletion (40 years versus 30 years, p <0.001), Figure 4.

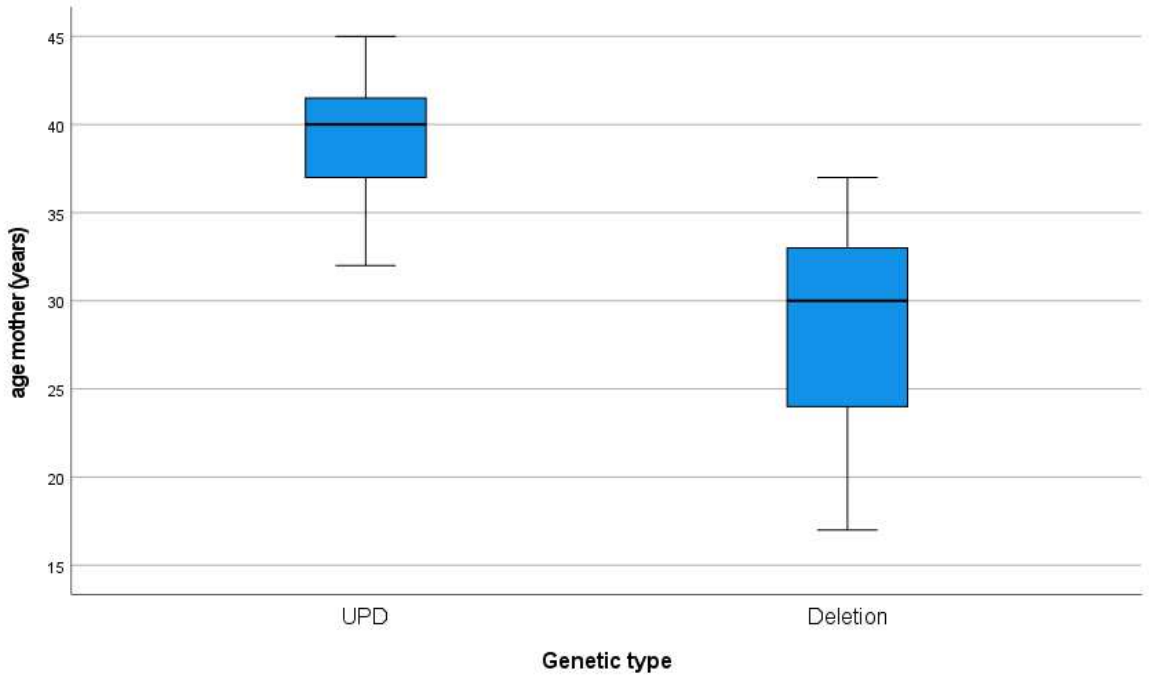

Figure 4 Maternal age in genetic subtypes

Gestational age and birth mode

The median Gestational age at birth was 38, with 30 being the minimum and 42 the maximum. In 2/22 documented cases, the birth was vaginal. In the remaining 20/22 cases, therefore representing 90.9%, the birth was via caesarean section.

APGAR Score

APGAR scores were documented in 12 cases, with a minimum of 5 at 1 minute and of 6 at 5 min. None of the individuals had a maximum of 10 points at 1 minute, the maximum was 9 points, and the median was 8. The median at 5min was 9 points.

Birth weight, length, and head diameter

Birth weight and length were documented in 28 cases and the SD could be calculated in 26 cases (

Table 8). Both were reduced, although birth weight SD more prominently than length SD, with a mean SD of -1.09. The mean birth length SD in this cohort was – 0,33SD. The head diameter was slightly larger, with a mean of 0,33SD. 3 out of 26 neonates, hence 11,5%, were considered SGA.

		Count	Missing	Mean	Median	Minimum	Maximum	SD
Age mother (years)		29	8	33	33	17	45	7
Age father (years)		29	13	38	37	30	45	5
Gestational age		29	3	37	38	30	42	3
Birth mode	missing	7						
	vaginal	2						
	Caesarean	20						
APGAR 1min		29	17		8	5	9	2
APGAR 5min		29	17		9	6	10	1
Weight at birth		29	1	2516	2570	1140	3200	503
Weight (SD)		29	3	-1,09	-1,00	-4,28	,57	,95
Length at birth		29	1	47,5	48,0	41,0	52,0	2,8
Length (SD)		29	3	-,33	-,23	-1,95	1,00	,83
Head diameter at birth		29	11	33,2	33,8	28,0	37,0	2,5
Head diameter (SD)		29	11	,39	,47	-1,03	2,03	,85
SGA	no	23						
	yes	3						

Table 8 Peri- and neonatal characteristics

Prenatal diagnostics

The data on prenatal diagnostics were difficult to analyse, as often no information was documented, and it was therefore difficult to assess whether no diagnostics

were carried out or whether they were simply not documented. Two cases of hydramnios and one case in which an amniocentesis was performed due to the mother's age were documented in Austrian data. However, the amniocentesis did not lead to a prenatal diagnosis of PWS.

3.1.5 Neonatal care

Neonatal care

Out of 29 neonates, 28 were hospitalized after birth for an average of 26 days. Due to the unavailability of detailed data on the duration of hospitalization and the administration of feeding tubes, it was not possible to record this information for all cases. The duration of hospitalization was recorded in only 13 cases, and the duration of tube feeding was recorded in 12 out of 29 cases, as shown in Table 9.

A feeding tube was required in 80% of cases, with a mean duration of 62 days. Unfortunately, the data on respiratory issues was limited. It did not indicate whether additional breathing measures were required in most cases. One patient received intensive care for six weeks and three received continuous positive airway pressure (CPAP). Five out of 9 received oxygen, however, oxygen administration was not documented in 20/29 cases. Information about other underlying conditions that would require intensive care was not collected.

		Count	Column N %	Missing	Mean	Median
Hospitalisation	no	1	3,8%			
	yes	25	96,2%			
Duration of hospitalisation in days		29		16	26	21
Feeding tube	no	4	20,0%			
	yes	16	80,0%			
Duration of tube feeding in days		29		17	62	42
Speech therapy	missing	11				
	no	6				
	yes	12				
Physiotherapy	missing	2				
	no	2				
	yes	25				
Occupational therapy	missing	9				
	no	3				

yes	17					

Table 9 Neonatal care and additional measures

Additional measures

In most cases, early interventions such as speech therapy, occupational therapy, and physiotherapy were initiated after diagnosis. Physiotherapy is administered in 25/27 cases (92,6%), occupational therapy in 17/20 cases (85%), and speech therapy in 12/18 (66,7%) of patients (Table 9). Although the exact time of initiation was often not documented, it was usually stated that they were initiated immediately after diagnosis.

3.1.6 Growth hormone administration

Growth hormone was administered in 27/29 cases (91.3%), whereas in one of the missing cases it was already planned to start therapy in the future. The median age at the start of treatment with GH was 24 months and the median delay from diagnosis until treatment was 14 months (Table 10).

		Count	Missing	Mean	Median	Minimum	Maximum	SD
Growth hormone	no	2						
	yes	27						
Age when GH was started (months)		29	2	33	24	2	178	35
Months between diagnosis and GH start		29	3	21	14	1	63	18

Table 10 Growth hormone therapy in Austria

3.2 Comparison with France

3.2.1 Comparing the age at diagnosis

The median age at diagnosis of PWS in France was 23 days, which is significantly lower than in Austria, where the median age at diagnosis is 52 days (Table 11). This difference is statistically significant ($p<0.001$), and thus, we reject the null hypothesis that the age at diagnosis is the same in Austria and France and assume that PWS is diagnosed earlier in France than in Austria.
Furthermore, even if we exclude the single case in Austria where the diagnosis was made at almost 14 years of age, the difference remains statistically significant.

		Age at diagnosis (d)						
		Count	Missing	Median	Minimum	Maximum	SD	Variance
Country	France	60	8	23	3	757	139	19241
	Austria	29	4	52	7	5062	1066	1135730

Table 11 Comparison of the age at diagnosis in Austria and France

There is also a significant difference in the delay between the initiation of genetic testing and the definite confirmation of diagnosis ($p<0.001$). In France, genetic testing takes a median of 10 days to complete, whereas in Austria it takes significantly longer, with 25 days. However, the maximum delay in France was 381 days, which is higher than in Austria (Table 12).
The time between birth and the initiation of genetic testing is also longer in Austria than in France. In Austria, the mean time until genetic testing is initiated is 15 days, while in France it is 7 days. However, this difference is not statistically significant.
Additionally, there is no significant difference in the frequency of the genetic subtypes.

			Count	Missing	Mean	Median	Minimum	Maximum	SD
Country	France	Delay until genetic test (d)	60	11	44	7	1	739	131
		Delay until results (d)	60	13	25	10	2	381	57
	Austria	Delay until genetic test (d)	29	8	451	15	1	5044	1160
		Delay until results (d)	29	8	46	25	6	224	58

Table 12 Comparison of the delay of genetic testing in Austria and France

3.2.2 Comparing perinatal factors and neonatal care

Maternal and paternal ages, as well as gestational age at birth, were similar in both countries. The maternal age was significantly higher in the UPD group in comparison to other causes in both countries.

A Caesarean section was statistically significantly more common in Austria than in France for the birth of PWS patients. Weight SD at birth was found to be similar as well between the two countries, however, length SD was significantly lower in France. However, It must be noted that different data sources were used to calculate the SD, and their validity when compared may therefore be limited. Especially since absolute birth height and weight, as well as gestational age, are not significantly different (Table 13).

There were no significant differences between Austria and France regarding the frequency or duration of hospitalization after birth, the use of tube feeding, and the duration of tube feeding or the frequency of physiotherapy, speech therapy, and occupational therapy. However, it should be noted that the occupational therapy evaluated here was equated with psychomotor therapy in France for the purposes of comparison. It can be assumed that the areas of activity overlap considerably, but it cannot be guaranteed that they are exactly the same in both countries.

		Country												
		France							Austria					
		Count	Missing	Mean	Median	Minimum	Maximum	SD	Count	Missing	Mean	Median	Minimum	Maximum	SD
Age mother (years)		60	4	33	33	20	44	6	29	8	33	33	17	45	7
Age father (years)		60	15	36	35	23	69	8	29	13	38	37	30	45	5
Gestational age		60	1	39	39	28	42	3	29	3	37	38	30	42	3
APGAR 1min		60	4	8	9	0	10	3	29	17	7	8	5	9	2
APGAR 5min		60	4	9	10	3	10	2	29	17	9	9	6	10	1
Birth mode	missing	2							7						
	vagnial	19							2						
	Cesaren	39							20						
Weight at birth		60	0	2584	2590	1110	3620	569	29	1	2516	2570	1140	3200	503
Weight (SD)		60	1	-1,23	-1,21	-2,78	,77	,83	29	3	-1,09	-1,00	-4,28	,57	,95
Length at birth		60	3	47,5	48,0	35,0	53,0	3,2	29	1	47,5	48,0	41,0	52,0	2,8
Length (SD)		60	4	-1,11	-1,15	-3,00	2,19	,95	29	3	-,33	-,23	-1,95	1,00	,83
Head diameter at birth		60	1	33,6	34,0	26,0	38,0	2,4	29	11	33,2	33,8	28,0	37,0	2,5
Head diameter (SD)		60	2	-,38	-,20	-3,20	4,89	1,54	29	11	,39	,47	-1,03	2,03	,85
SGA	no	39							23						
	yes	17							3						
Hospitalisation	missing	0							3						
	no	4							1						
	yes	56							25						
Duration of hospitalisation in days		60	8	45	33	4	160	38	29	16	26	21	10	55	15

		Country												
		France							Austria					
		Count	Missing	Mean	Median	Minimum	Maximum	SD	Count	Missing	Mean	Median	Minimum	Maximum	SD
Feeding tube	missing	2							9						
	no	9							4						
	yes	49							16						
Duration of feeding tube in days		60	16	64	38	2	195	57	29	17	62	42	1	240	67
Physiotherapy	missing	9							2						
	no	7							2						
	yes	44							25						
Occupational therapy	missing	23							9						
	no	16							3						
	yes	21							17						
Speech therapy	missing	13							11						
	no	26							6						
	yes	21							12						

Table 13 Comparison of perinatal factors and early care

3.2.3 Comparing growth hormone treatment

The median age of GH treatment start is 11 months in France and the aforementioned 24 months in Austria (see Table 14). The difference is statistically significant ($p<0.05$) but can be partly explained by the generally earlier age at diagnosis and therefore earlier treatment start in France. The difference in the delay between diagnosis and the start of GH treatment is not statistically significant. In France, the median delay from diagnosis to start of GH treatment is 11 months, in Austria it is slightly higher at 14 months.

In Austria, 27/29 patients (93.1%) with PWS received GH, whereas in France the frequency of GH administration was significantly lower at 40%. This difference was also statistically significant ($p<0.001$) in the chi-squared tests.

				Count	Missing	Mean	Median	Minimum	Maximum	SD
Country		Growth hormone	no	30						
	France		yes	20						
		age when GH was started (months)		60	42	12	12	7	23	5
		months between diagnosis and start GH		60	45	12	11	6	23	5
	Austria	Growth hormone	no	2						
			yes	27						
		age when GH was started (months)		29	2	33	24	2	178	35
		months between diagnosis and start GH		29	3	21	14	1	63	18

Table 14 Comparison of growth hormone treatment

4 Discussion

Age at diagnosis

This study is, to our knowledge, the first to assess the age at diagnosis, early care, and growth hormone treatment in PWS patients in Austria.

With a median age at diagnosis of 52 days and 68% of patients diagnosed within the first three months (90 days) of life, diagnosis in Austria is still made relatively early and in accordance with reference literature, which displays a range of median age at diagnosis from 18 days (1) to 4 months (63), to approximately half a year (65).

However, the direct comparison with France also indicates that there is still room for improvement. The results show that children with PWS are diagnosed significantly earlier in France than in Austria. 52 days is the median age at diagnosis in Austria compared to 23 days in France, thus displaying a difference of almost one month in median age at diagnosis. Furthermore, 5/25 children (20%) were diagnosed after 1 year and 3 of these (12% of all) were diagnosed after 3 years of age.

Bar et al. state that in their study, late diagnosis occurred either because of false-negative FISH when used as a first-line test or because of failure to recognise early symptoms in neonatology. (1)

In our study, we found a significant delay due to genetic testing. While genetic testing in France takes a median of 10 days (from sample collection to genetic results), the median delay in Austria is 25 days, significantly longer, which certainly contributes to the later diagnosis.

As the time to initiate genetic testing is also longer in Austria (15 versus 7 days), although not statistically significant, it is likely that a combination of the longer time to genetic analysis and the later a priori suspicion of PWS may ultimately explain the later diagnosis in Austria. This is further supported by the fact that in the 5 children diagnosed after the age of 1 year, the delay caused by genetic testing was not exceptionally long. This also suggests that particularly late diagnoses are more likely to be caused by late suspicion rather than by a long duration of genetic testing.

Although there was no significant difference in age at diagnosis between the group born before 2013 and those born after 2013, genetic testing has evolved since the start of the survey period and is now more widely available.

Genetic subtypes

The frequency of the genetic subtypes found in this study (deletion at 58,6%, UPD was seen in 31%, and an Imprinting centre defect in 3,4%) corresponds to those mentioned in the literature. (69) In a multisite cohort study by Butler MG et al. the analysis of genetic data from 510 patients with PWS showed frequencies, very much like those observed in our study. 303 of 510 individuals (60%) had a deletion, 36% a UPD, and 4% an imprinting defect. (69) The frequencies in our reference study (deletion in 53%, UPD in 42%, IC defect in 2%) (1) are also in accordance with the observed genetic subtypes in this study.

Pre- and perinatal parameters

We can also confirm the existing observation that the average age of mothers of PWS children with UPD is significantly higher than that for other genetic causes. (8,69) In this case, the average age in the UPD group is 40 years compared to 30 years in the deletion group. A similar difference was also observed in France (38 years in the UPD group versus 31 years in neonates without UPD). (1) This difference in maternal age can be expected and is most likely caused by the underlying genetic mechanism and disturbance of meiosis (8,17,69).

The median gestational age at birth in our study was 38 weeks, with a minimum of 30 and a maximum of 42 weeks. This is also in accordance with other studies, showing a mean gestational age of approximately 38-39 weeks. (66,70,71). However, it should be noted that the weeks of gestation in this study were rounded up to the nearest full week and may therefore be slightly overestimated.

Individuals with PWS generally have a higher rate of caesarean sections than the healthy population. (72) This is most likely due to a higher prevalence of pregnancy complications, breech position, decreased foetal movement, and possibly an impaired labour progression caused by a lack of oxytocin. (12,73) In this study, only 2 of the 22 documented cases were vaginal births, whereas the other 20 (90.9%), were caesarean sections. This frequency exceeds other studies so far, as reported frequencies of Caesarean sections were usually around 40-60%. (12,15,71,72) The rate of caesarean sections in the reference publication from France was slightly higher at 67%. (1)

In terms of perinatal parameters, birth weight, and birth length were both reduced in this study, although the birth weight SD, with a mean of -1.09 SD, was more

markedly affected than the length SD. The length SD was also significantly lower in France, which may be due to the different data sources used to calculate the SD, especially as absolute birth length and weight are not significantly different in the two countries. The observation, that predominantly birth weight is reduced has been previously reported by other studies (12,74) and suggests a more pronounced impairment in prenatal nutrition than in growth. (74)

Early care

Due to the frequent symptoms, such as hypotonia, poor suck, and difficulty feeding, the vast majority of newborns need to be hospitalized after birth and require feeding via tube. (12,14,15,18) This was also found in our study, in which 96% of infants were hospitalized for an average duration of 26 days and 80% required a feeding tube with an average administration duration of 62 days. Those rates of hospitalisation and tube feeding are in line with other studies and the reference publication by Bar C et al. (1,12,14,15,18) There was no significant difference in the duration of neither hospitalisation or tube feeding between patients in Austria and France.

The high rate of post-diagnostic physiotherapy initiations of 92,6% in Austria stands out particularly positively. Along with the rate of occupational therapy, which is prescribed in 85% of cases after diagnosis. Speech therapy is also administered in the majority of individuals, however with 67%, less frequent than the other two therapies. This result was also observed in the reference study, where physiotherapy was administered in 75%, psychomotor therapy in 57%, and speech therapy in 45%. (1) Bar C et al. already highlighted that in their discussion and emphasised the need for an assessment of oral skills and the prescription of speech therapy for these infants, along with physiotherapy and psychomotor therapy. (1)

Although not statistically significant, the generally lower frequencies of these therapies in France compared to Austria might also be due to their earlier age at diagnosis in France.

GH treatment

Growth hormone was authorised for use in Austria in 2000 and has since become widely used. At the time of data collection, 93.1% of the analysed patients were already receiving GH treatment, with treatment starting at a median age of 2 years.

In France, treatment is initiated at the median age of 11 months and therefore significantly earlier. As already explained in Chapter 1.1.7, the literature considers starting treatment as early as possible, ideally within the first year of life, to be particularly favourable. (53,60-62) The aim should therefore be to reduce the median time between diagnosis and the start of GH treatment to less than a median of 14 months and to initiate treatment within the first year of life and optimize motor and mental development, general development, and body composition. (53,60-62) In the French cohort, where only 40% of patients receive GH treatment, the frequency of GH administration is significantly lower compared to Austria. This is likely attributable to the significantly earlier diagnosis observed in France and the overall younger age of the included patients. In their study, Bar C et al. observed that patients without GH treatment had a lower mean age compared to those who received GH treatment (1), which supports the assertion that early diagnosis is responsible for the lower frequency of GH administration. Moreover, studies utilising the French database for PWS have demonstrated a rate of GH administration of approximately 86% in a study group more comparable to the Austrian cohort. (27,67)

4.1 Weaknesses and limitations of this study

One of the main limitations of this study arises from the limited number of available cases. Austria is a relatively small country with a smaller population than France, which leads to small sample sizes and limits the available case numbers when studying a rare disease like Prader-Willi syndrome. This also led to unequal group sizes when comparing the data with France, a country with a much larger population, and made it necessary to include a wider age range. This is the reason, why data from Austrian PWS patients, who were born between 2000 and 2021, was compared with data from French patients born in 2012 and 2013.

Besides the limitation in data quantity, the cases were also documented with varying degrees of accuracy, making it difficult to collect complete data sets for some parameters. This was particularly true for data from the Department of Paediatric and Adolescent Medicine at the University Hospital of Salzburg, as initial postnatal care and early therapeutic measures were often carried out in peripheral clinics and

patients were only referred to the reference centre at a later stage. It is therefore possible that data was not included because it was not documented in the first place. Additionally, to the missing data, it cannot be ruled out that, despite utmost care, data may have been overlooked or incorrectly transmitted during data collection.

As the data collection only included patients treated at the Department of Paediatric and Adolescent Medicine at the University Hospitals of Graz and Salzburg, an undercoverage bias must be expected and it cannot be assumed that all data in all regions of Austria are represented completely. Specifically, regions such as Burgenland, Carinthia, Vorarlberg, Tyrol, and Vienna may be underrepresented as only a maximum of two patients from these regions were included. This is especially applicable to Vienna, which is the capital and a densely populated region of Austria.

4.2 Outlook and remaining questions

Since this study states, that the delay in diagnosis in Austria is at least partially due to the duration of genetic tests, a logical next step would be to find out why genetic analysis takes longer in Austria than in France. This raises the question of which molecular biological methods are usually used for diagnosis and whether the delay is caused directly by the method used or already occurs beforehand, during delivery to the laboratory. A detailed investigation into the causes of the two cases in this study, in which the genetic tests were delayed for more than six months, could provide insights into how to avoid such delays in the future.

To evaluate the role of later recognition of symptoms in particularly late diagnoses, an investigation of the 5 cases with late diagnoses in this study should be considered. This could show whether the absence or non-recognition of symptoms in the neonatal period was the reason for such a late suspicion of PWS.

Another approach would be to compare the total number of genetic tests requested for PWS with the number of positive tests to assess whether the indication for genetic testing is less strict and applied more quickly in France than in Austria.

It remains unclear why the rate of caesarean sections in Austria is so high compared to other studies. An assessment of pregnancy complications and an investigation of the reasons for these caesarean sections could help to resolve this question.

Regarding GH administration, an assessment of the necessary steps before starting treatment could help to understand the factors contributing to the 14-month gap between diagnosis and treatment initiation. Given the positive effects of an early treatment start, we should aim to avoid unnecessary delays in GH treatment initiation. A broader understanding of the reasons for the delay could pave the way for more efficient processes and ensure the earliest possible treatment for future patients.

In general, we should aim for consistent documentation, as it sets the foundation for future research by providing more structured and thorough data. Especially when studying rare diseases, a detailed data record simplifies research and ensures the best possible utilization of the limited data available.

4.3 Conclusion

The initial question of this study was to assess the status quo of Prader-Willi diagnosis and early intervention in Austria. We can now conclude that overall, this study gives a relatively positive picture, especially with regard to GH therapy and the initiation of physiotherapy, occupational therapy, and speech therapy. In terms of the age of diagnosis, Austria, with a median of 52 days, can keep up with most other countries. However, the comparison with France shows that there is still room for improvement. Further studies are necessary to evaluate and improve diagnosis, reduce the time to start growth hormone treatment, and ultimately ensure the best possible outcome for all patients with Prader-Willi syndrome.

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