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The use of medical care and the prevalence of serious illness in an adult Prader–Willi syndrome cohort

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ABSTRACT

Introduction: Adults with Prader–Willi syndrome (PWS) have an increased occurrence of several medical conditions. We report on the consequences of high morbidity rates such as prevalence rate of hospital admissions, medication use and surgery in a Dutch cohort of adults with PWS. Special attention is paid to causes and symptoms of serious illness.
Method: Participants were contacted via the Dutch Prader–Willi Parent Association and through physicians specializing in persons with ID. The persons with PWS and their main caregivers were visited at home. Information was collected through semi-structured interviews on 102 adults with PWS.
Results: The need for medical care in the neonatal period is associated with hypotonia and feeding problems. Hospital admissions for respiratory tract infections are frequent. During childhood most hospital admissions were due to PWS syndrome specific surgery. During adolescence hospital admissions occurred for scoliosis surgery and endocrine evaluations. At adult age, hospitalization was associated with inguinal hernia surgery, diabetes mellitus, psychosis, erysipelas, water and drug intoxications. In the older group, respiratory infections were again the main reason for hospital admissions. Frequently used medications at adult age included psychotropics, laxatives, anti-diabetics and dermatologic preparations. Abnormal drinking patterns, problems with anesthesia, decreased ability to vomit, abnormal pain awareness and unpredictable fever responses were frequent and often lead to delayed diagnoses of serious conditions.
Discussion: People with PWS are frequent users of medical-care. Reasons for hospitalization and medication use are age specific. Knowledge on the different presentation of symptoms in people with PWS is needed. In case of unexplained illness, disturbances of consciousness and behavioral changes in people with PWS, an infection should be ruled out in the first place. Information from this study may help in preventing conditions and recognizing conditions in an early stage. Adequate preventive management and treatment of PWS related morbidity, could reduce medical care use in the long term and could improve quality adjusted life years.

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1. Introduction

Prader–Willi syndrome (PWS) is a neurodevelopmental disorder due to a genetic abnormality on chromosome 15 [1–3]. PWS is characterized by extreme neonatal hypotonia at birth with failure to thrive and a range of physical, behavioral, cognitive and psychiatric characteristics that become apparent during later life and give rise to often complex health and social needs [4].

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Exhibit 2068
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A number of studies have contributed to the knowledge on physical and psychiatric morbidity [5–13]. Adults with PWS have an increased occurrence of several medical conditions such as diabetes mellitus, hypertension, leg edema, skin infections and respiratory infections, psychosis and mood disorders [5–13]. These physical health problems may be followed by an increased use of medical care. However, relatively few systematic studies on these characteristics are available [7,14].

Signs and symptoms of illness are not always easy to interpret in people with PWS. A high pain threshold, decreased ability to vomit and temperature instability are frequently mentioned as characteristics of the syndrome [4], and may mask signs and symptoms of illness. However, only little systematic data on these characteristics in a large cohort are available [15,16].

The aim of this study was to describe hospital admissions, medication use, undergone surgery, problems with anesthesia and recovery from illness in a Dutch cohort of adults with PWS. Special attention is paid to the causes and symptoms of serious illness. This information could provide clues about factors influencing life expectancy in PWS. We hope to find factors that contribute to the development of guidelines for preventive management.

2. Method

2.1. Procedure

The current study is part of a large study on the physical, behavioral and psychiatric characteristics of adult with PWS. Persons with possible PWS were contacted through the Dutch Prader–Willi Parent Association and through physicians specializing in ID. Information was collected through interviews with the individuals with PWS and their main carers (family and/or professional carers) at home. They were interviewed using semi-structured interviews that included questions about physical health problems experienced over the participants' lifetime. Detailed information on hospital admissions, medication use, surgery, and serious illness was also collected. Medical files were, with permission of those concerned, retrieved from attending physicians. The current study was part of a large study in The Netherlands on "Ageing in PWS" and was approved by the Medical Ethics Committee Maastricht.

2.2. Genetic diagnosis

Parents were asked whether genetic tests on PWS including genetic subtype had been undertaken previously. Written confirmation on genetic diagnosis was requested from genetic centers, with permission of the legal representatives. In participants who did not have a confirmed genetic diagnosis ($n = 40$), genetic testing was undertaken. Cytogenetic and molecular analysis using the SALSA MLPA kit P245 (MRC Holland, Amsterdam) was performed to establish whether a deletion was present. Diagnosis of PWS was confirmed by DNA methylation studies on the SNURF/SNRPN locus and mUPD was confirmed with microsatellite analysis at various loci on chromosome 15, when blood of parents was available. If a deletion was rejected by MLPA and an mUPD was rejected by microsatellite analysis, an imprinting defect was assumed.

2.3. Participants

In total 149 nominees with a (possible) diagnoses of PWS were notified to us. After eliminating those nominees who had died and those whose parents informed us that PWS had been excluded by genetic testing, 145 possible participants were left. Of these, 108 agreed to participate in the study (response rate 75%). The participants underwent genetic laboratory testing before ($n = 68$) or during the study ($n = 40$) to confirm the diagnosis and determine the genetic subtype. For 102 participants, the genetic diagnosis of PWS was confirmed and therefore this report is based on these 102 individuals.

Of the 102 adults with PWS who were included in this study, 49 (48%) were male. Their mean age was 36.2 yr (SD 12.4, range 18–66 yrs). Of all participants 55 had paternal deletion (54%), 44 had mUPD (43%) and three participants had an imprinting centre defect (3%). The mean age at (genetically confirmed) diagnosis in the cohort was 24.7 yr (SD 15.7, range 0–65 yr). The mean age at diagnosis was significantly lower in the younger age groups than in the older age groups (<25yrs: 6.9 yr, 25–34: 17.0 yr, 35–44 yr: 31.7 yr, >45 yr 41.1 yr; ANOVA: $p < 0.05$). Eighty-one (79%) participants lived in institutional residential or community residential facilities while 20 (20%) participants lived at home with their parents or family, one (1%) participant lived independently with some professional support. The level of ID was mild (49%, $n = 50$) or moderate (28%, $n = 29$) in most participants. Eight (8%) participants

Table 1
Most frequent reasons for hospital admissions according to life stage (total $N = 102$).

	0–2 yr ($n = 102$)	3–9 yr ($n = 102$)	10–19 yr ($n = 102$)	20–39 yr	40+ yr ($n = 45$)
1	Hypotonia, feeding problems ($n = 87$)	Tonsillectomy ($n = 13$)	Orchidopexia/inguinal hernia ($n = 21$)	Inguinal hernia ($n = 7$)	Respiratory infections ($n = 5$)
2	Respiratory infections ($n = 13$)	Orchidopexia/inguinal hernia ($n = 12$)	Scoliosis ($n = 10$)	Diabetes mellitus ($n = 5$)	Cerebrovascular accidents ($n = 4$)
3	Other infections ($n = 11$)	Strabismus surgery ($n = 11$)	Endocrine investigations ($n = 8$)	Psychiatry ($n = 5$)	Inguinal hernia ($n = 3$)
4	Diagnostics ($n = 11$)	Ear tube surgery ($n = 7$)	Strabismus surgery ($n = 5$)	Intoxications (water/medication) ($n = 4$)	Water intoxication ($n = 3$)
5	Strabismus surgery ($n = 6$)	Diagnostics ($n = 7$)	Accidents ($n = 4$)	Erysipelas ($n = 3$)	Low body temperature ($n = 2$)
6	Muscle biopsy ($n = 5$)	Infections ($n = 5$)	Tonsillectomy ($n = 4$)	Cholecystitis ($n = 3$)	Erysipelas ($n = 2$)
7	Orchidopexia/inguinal hernia ($n = 5$)	Congenital abnormalities[a] ($n = 5$)	Infections ($n = 4$)	Fractures ($n = 3$)	Dental care ($n = 2$)
8	Congenital abnormalities[a] ($n = 4$)	Accidents ($n = 3$)	Appendicitis ($n = 3$)	Accidents ($n = 3$)	Diarrhea/obstipation ($n = 2$)
9	Convulsions ($n = 3$)	Appendicitis ($n = 1$)	Psychiatry ($n = 2$)	Knee surgery ($n = 3$)	Anemia ($n = 2$)
10	Tonsillectomy ($n = 2$)	Convulsions ($n = 1$)	Kidney surgery ($n = 2$)	Sterilization ($n = 1$)	Trombosis/lung embolism ($n = 1$)

[a] Congenital abnormalities include e.g. kidney abnormalities, cheiloschisis, club feet, lob ears, string of the tongue, phimosis, and hypospadias.

had severe ID. The other participants were functioning on a borderline ID level (10%, $n = 10$) or did not have ID (5%, $n = 5$). Mean body mass index (BMI = kg/m^3) was 32.2 (SD 7.9, range 16.8–51.9). Fifty seven (56%) participants were obese (BMI $\geq$ 30). Mean BMI did not differ statistically significant between genetic subtypes.

2.4. Statistical analyses

To test whether differences between genetic subtypes, age(-groups), and BMI(-groups) were statistically significant, Chi-square tests and independent samples *t*-tests were performed. SPSS (version 16.0) was used to analyze the data. All tests were two-tailed, and *p*-values of 0.05 or less were considered statistically significant.

Table 2
Number of adults with PWS using medication according to ATC code, tract and medication group.

ATC	Tract	Medication group	*N*
A	Alimentary tract and metabolism	A02 Antacids	12
		A06 Laxatives	23
		A07 Intestinal antiinflammatory agents	1
		A08 Anti-obesity preparations	1
		A10 Drugs used in diabetes	15
		A11 Vitamins (vitamin D)	4
		A12 Mineral supplements (calcium)	4
		A16 Other alimentary tract and metabolism products	1
		Total	61
B	Blood	B01 Antithrombotic agents	6
		B03 Antianemic preparations	4
		Total	10
C	Cardiovascular system	C01 Cardiac therapy	1
		C02 Antihypertensives	8
		C03 Diuretics	2
		C10 Lipid modifying agents	12
		Total	23
D	Dermatologica	D07 Corticosteroids, dermatological preparations	14
		Total	14
G	Genito urinary tract, sex hormones	G04 Urologicals	1
		G03 Sex hormones G03B Androgens	8
		G03C Estrogens	7
		G03D Progestogens	6
		Total	22
H	Systemic hormonal preparations	H01 Hypothalamic hormones	7
		H02 Corticosteroids for systemic use	1
		H03 Thyroid therapy	7
		Total	15
J	Antiinfectives for systemic use	J01 Antibacterials	6
		Total	6
M	Musculo-skeletal system	M05 Drugs for treatment of bone diseases	3
		Total	3
N	Nervous system	N02 Analgesics	5
		N03 Antiepileptics	15[a]
		N04 Anti-parkinson drugs	1
		N05 Psycholeptics N05A Antipsychotics	30
		N05B Anxiolytics	2
		N05C Hypnotics and sedatives	8
		N06 Psychoanaleptics N06A Antidepressants	15
		Total	76
R	Respiratory system	R01 Nasal preparations	1
		R03 Drugs for obstructive airway diseases	7
		R05 Cough and cold preparations	2
		R06 Antihistamines for systemic use	10
		Total	20
S	Sensory system	S01 Ophthalmologicals	2
		S02 Otologicals	2
		Total	4

[a] 13 out of 15 persons used antiepileptics because of mood-stabilizing effects, not because of epilepsy.

3. Results

For more detailed information about physical health problems, behavior and psychiatric illness in this cohort, we refer to our recent papers [17–19].

3.1. Hospital admissions

Most people with PWS were admitted to hospital in their first year ($n = 95$) (mean age 0.5 yr, range 0–15 yr, SD 2.0). Neonatal hypotonia and feeding problems were reasons for stay in hospital in 87 out of 95 informative cases. In seven older individuals, whose parents had died, information regarding the neonatal period was lacking. The mean duration of this first hospital admission was 9.5 weeks (range 1–48 weeks, SD 8.6). In the remaining 7/95 cases, first hospital admissions were related to diagnostic tests, strabismus surgery, tonsillectomy, cerebrovascular accident and club foot surgery.

The mean number of total hospital admissions was 4.0 (range 0–12, SD 2.3). We did not find statistically significant relationships between the number of hospital admissions on the one hand and age, genetic subtype and BMI on the other hand. The reasons for hospital admissions in the different life stages are summarized in Table 1. Fourteen persons had been admitted to general or psychiatric hospitals because of psychiatric illness, mostly because of affective disorders with or without psychotic symptoms. However, although psychiatric episodes were common, they were mostly treated in the community.

3.2. The use of medication

Medication usage at the time of the study is described in Table 2. Twenty persons did not use any medication, 20 persons used one preparation, 46 used 2–5 different medications and 16 used five or more different medications. The Anatomical Therapeutic Chemical Classification System (ATC) was used to categorize different medication groups. Medication groups which were used most frequently included psychotropics ($n = 30$), laxatives ($n = 23$), anti-diabetics ($n = 15$), antiepileptics ($n = 15$) and dermatologic preparations ($n = 14$).

The use of sex hormones is summarized in Table 3. Of the men, 15 out of 49 had a history of sex hormone replacement. Medical

Table 3
Number of persons who are taking (or had been taking) hormone replacement.

	N
Prescribed thyroid hormone	
Lifetime history	9
Current prescription	7
Prescribed growth hormone	
Lifetime history	13
Current prescription	5
Prescribed sex hormone	
○ Male	
Lifetime history	15
Current prescription	8
○ Female	
Lifetime history	14
Current prescription	9
Prescribed adrenal hormone	
Lifetime history	1
Current prescription	1

reasons to start hormone replacement included the risk of osteoporosis, the possible effect on secondary sex characteristics, the possible effect on cryptorchidism and the possible effect on behavior. Seven individuals discontinued replacement therapy because of either behavioral problems, having reached the desired effects, or development of skin problems (acne and skinpicking). Fourteen women had a history of sex hormone replacement therapy. The medical reasons to start the therapy included the risk of osteoporosis, the regulation of menstrual cycle and/or contraception. Five individuals stopped replacement therapy because of the development of thrombosis, weight increase and/or behavioral problems. Seven of the women used progesterone in order to regulate their menstrual cycle and/or for contraception.

Table 4
Number of adults with PWS according to tract and reasons for surgery.

Tract	Surgery	*N*
Cardio-vascular	Varicose veins	2
	Total	2
Endocrine	Parathyroid	1
	Testicular carcinoma	1
	Total	2
Gastro-intestinal	Appendectomy	5
	Cholecystectomy	3
	Umbilical hernia	2
	Intestinal surgery	1
	Hemorrhoids	1
	Oesophagoscopy to remove a foreign body	1
	Gallstone crushing	1
	Total	14
Uro-genital	Orchidopexy (in males)	32
	Inguinal hernia	23
	Orchiectomy	4
	Sterilization in woman	3
	Kidney/urinary tract surgery	2
	Circumcision	2
	Hypospadias	1
	Placement of testicular prosthesis	1
	Phimosis	1
	Total	69
Musculo-skeletal	Scoliosis	11
	Hip surgery	4
	Arthroscopy	4
	Knee surgery	3
	Osteosynthesis	3
	Foot surgery	3
	Total	28
Eyes	Strabismus	21
	Cataract	2
	Retinal detachment	2
	Total	25
Ear, nose, throat	Tonsillectomy	17
	Ear tubes	9
	Nasal septum	2
	Palate	1
	Cleft lip	1
	Acoustic duct	1
	Lop ears	1
	Total	32
Dental	Element extraction	6
	Wisdom teeth	4
	Total dental extraction	3
	Jaw surgery	1
	Total	14
Other	Muscle biopsy	4
	Burns	1
	Breast reduction	1
	String of the tongue	1
	Atheroma	1
	Ganglion cyst	1
	Abscess	1
	Total	10

3.3. Surgery

Types of surgery are summarized in Table 4. Thirteen persons had no history of surgery. Twenty-seven persons had had one type of surgery, 32 persons two types, 21 persons three types and nine persons more than three types. Most frequent surgery was for orchidopexy ($n = 32$) and inguinal hernia surgery ($n = 23$) in men, strabismus ($n = 21$), tonsillectomy ($n = 17$), scoliosis ($n = 11$), ear tubes ($n = 9$) and dental problems ($n = 6$).

3.4. Problems with anesthesia

Thirteen persons had had problems relating to anesthesia. Most prominent ($n = 6$) was a delayed time to wake up after surgery as a prolonged and exaggerated response to sedatives. Other problems included cardiac events ($n = 3$), of whom two persons endured a cardiac arrest, unstable glucose levels ($n = 2$); pain sensation during surgery ($n = 1$); intubation problems because of anatomical abnormalities ($n = 1$); adrenal insufficiency ($n = 1$); and dyspnea ($n = 1$).

3.5. Serious illnesses

In total, 38 out of 102 persons experienced at least one episode of serious or life threatening illness, as reported by the parents or caregivers. These events were not related to age, genetic subtype or BMI. The causes of these illnesses are described in Table 5. Table 6 shows factors which may be related to the recognition of illness such as an irregular drinking, vomiting, pain threshold and temperature instability.

4. Discussion

In this report, results are presented regarding the use of medical care and the prevalence of serious illness in a Dutch adult PWS cohort. This mainly relates to hospitalization rates, medication use, surgery and visits to the emergency department. We discuss the implications for services providing medical care for people with PWS with regard to prevention and early recognition of serious illnesses.

4.1. Hospital admissions

With regard to hospital admissions, the results in this study highlight age-specific causes of morbidity and hospitalization. In

Table 5
Number of adults with PWS according to causes of serious illnesses.

Cause of serious illness ($n = 40$)	*N*
Infection (mostly respiratory)	10
Intoxication/side effect medication	3
Diabetes mellitus	3
Apnea	2
Anemia	2
Kidney problems	2
Meningitis/encephalitis	2
Psychiatric problems	2
Adrenal insufficiency	1
Low body temperature	1
Near drowning	1
Cardiac arrest during anesthesia	2
Dehydration	1
Water intoxication	3
Bowel obstruction	1
Testicular carcinoma	1
Edema	1
Unknown	2

Table 6
Factors in recognizing illness.

Factors in recognizing illness	*N*
Irregular drinking pattern	
Yes	13
No	89
Vomiting	
Never	60
Once/rarely	41
Normal frequency	1
High pain threshold	
No	3
Yes	99
No pain expressed in cases of	
Toothache	60
Burns	49
Bruises	88
Sprains	46
Fracture	25
Temperature regulation	
Absence of fever during illness/infection	66
Fever above 40 °C	25
Low body temperature	9
Problems assessing temperature of the environment	
Yes	75
No	27

recent years, severe neonatal hypotonia has continued to lead to hospital admissions and need for tube feeding [20] and the diagnosis of PWS is often established within the first weeks of life. In the past, hypotonia during the neonatal period has often led to extensive medical evaluations including muscle biopsies and long term stay in hospital. Improved medical care has led to much lower mortality rates in the first year of life [8]. A further decrease in early infancy hospitalization rates and duration may be achieved by preventing severe respiratory infections by, for example, rigorous treatments with antibiotics [8,21]. In our study population, most hospital admissions during childhood were for PWS syndrome specific surgery such as orchidopexia, inguinal hernia, strabismus, tonsillectomy and the insertion of grommets. Scoliosis surgery and endocrine evaluation were common during adolescence. At adult age, hospitalization in our study population was associated with inguinal hernia surgery, diabetes mellitus, psychosis, water and drug intoxications and erysipelas. In older persons with PWS, respiratory infections were again the main reasons for hospital admissions. Cerebrovascular accidents and low body temperature also sometimes played a role in our experience. Most hospital admissions could not be prevented. However, awareness of possible physical health problems (e.g. erysipelas, respiratory infections) may contribute to a diagnosis in an earlier stage and may shorten the length of stay in the hospital.

4.2. Medication use

The high prevalence in the use of medication reflects the high morbidity in this group [19]. Frequently used medications included laxatives, anti-diabetics and dermatologic preparations. Most striking, however, is the prescription of psychotropics. Psychiatric problems play an important role in the health status and quality of life in adults with PWS because they are common and usually have a chronic course. Especially the mUPD subtype is known to be associated with psychiatric illnesses [10,12,13,22]. Close supervision and documentation of the prescribed medication is essential because side effects and intoxication are frequent in our experience. Therefore, we recommend that consultant psychiatrists specializing in persons with PWS should be contacted when psychotropics are started. Sex hormone replacement was less commonly used than expected based on recent recommendations [23]. Prescriptions easily add up and medication seeking by people with PWS is prominent in some individuals and can result in significant polypharmacy. In our experience, many people with PWS are inflexible regarding their medication regimes, at least partly because liquid medications tend to be sweet (e.g. laxatives and cough syrup) and they vigorously resist changes in routine. The possibility of this kind of behavior should always be taken into account while prescribing medication. We recommend a yearly medication review to minimize side effects, prevent drug interactions or overmedication.

4.3. Surgery and anesthetic problems

Surgery was mostly associated with the main characteristics of the syndrome. This is in line with findings in the literature [4,7]. PWS is known to be associated with higher anesthesic risks, associated with obesity, hypotonia, temperature instability, thick saliva and post anesthesic drowsiness. Therefore, anesthesia should be carefully monitored. Food seeking and other behavioral problems during hospitalization and complications due to skinpicking should always be taken into consideration when planning surgery [24–26]. The surgical team should also be aware of osteopenia in case of orthopedic problems.

4.4. Causes of serious illness

This report documents the occurrence of critical illnesses during the entire lifespan of people with PWS. Certain medical causes should be considered in case of unexplained illness, disturbances of consciousness and behavioral changes. First of all, sources of infection (mostly respiratory, but also gastro-intestinal or skin) should be ruled out, even in the absence of fever [27]. Besides, treating physicians should check for diabetic dysregulation, anemia (possibly due to rectal skinpicking), low body temperature, abnormal drinking patterns (water intoxication/dehydration), cardiac problems, adrenal insufficiency and adverse reactions to medication [9,28–31]. Due to the cross-sectional design of the study, frequency and mortality caused by disorders such as cancer or gastric dilatation, may have been underestimated.

Life events appear to be a contributing factor in the onset of major psychiatric disorders such as mood disorders and psychoses [12,13,19]. Presenting symptoms of psychiatric disorders in people with PWS in our experience include mood lability, suicidality, aggression, increased irritability and self harm. Behaviors associated with psychiatric disorders in people with PWS may lead to physical complications such as water intoxication, attempts to swallow inedible objects, severe self-harm, suicidal thoughts, coprophagia, rectal skinpicking and refusal to eat, drink or move. Therefore when faced with physical complaints, professionals should exclude psychiatric disorders as a possible cause. However, the opposite also holds true: a physical disorder could also trigger the development of a psychiatric disorder.

4.5. Recognizing illness

Complaints and symptoms are not always easy to interpret in persons with PWS. On the one hand, a decreased ability to vomit, abnormal pain awareness and unpredictable fever response can lead to underreporting of pain and missed diagnoses of serious conditions that would normally be expected to produce severe pain or fever. On the other hand, individuals with PWS frequently express somatic complaints for which objective evidence is lacking. When there is a marked discrepancy between objective findings and subjective stress, discomfort, or functional impairment,

malingering (pretending to be ill) should be considered, motivated by the possibility of obtaining food or avoiding tasks. Caregivers and physicians should be aware of these difficulties and should document which characteristics are medical alerts in a particular individual.

4.5.1. Abnormal pattern of eating and drinking

Hyperphagia is prominent in almost all adults with PWS. Therefore, individuals with PWS who show a decreased interest in food should also be suspected of suffering from a serious physical or psychiatric disorder. Thirteen persons in our cohort were reported to show an abnormal drinking pattern during certain periods. These episodes were related to diabetes ($n = 7$), lack of satiety ($n = 3$), behavioral problems ($n = 2$) and psychosis ($n = 1$). In three cases this led to water intoxication. Unusual water intake has not been researched in great detail in the literature. Akefeldt [28] suggests that this might be part of the typical overeating behavior or be a part of the hypothalamic impairment. Water intake in individuals with PWS should always be monitored because of the risk of developing hyponatraemia.

4.5.2. Inability to vomit

A commonly reported feature of PWS is a decreased ability to vomit with a complete absence of "natural" or induced vomiting noted in a large proportion of individuals [16]. The reasons for this are not completely known. The majority of the participants in our study had never vomited. The remaining individuals only vomited in rare circumstances, mostly only once during their life. Such circumstances included gastroenteritis, binge eating episodes, anesthesia, diabetic deregulation, alcohol consumption, psychiatric problems, serious infections and self generated vomiting. Caution is needed regarding reliance on emetic agents in the treatment of accidental poisoning for individuals with PWS since the response may be inadequate and higher doses of antiemetics could potentially be toxic. In case of complaints of nausea and/or vomiting, abdominal discomfort, dyspnea and distended abdomen, especially after a known episode of binge eating, the diagnosis of gastric dilatation should be considered [32].

4.5.3. Pain sensation

Decreased peripheral and deep pain sensation is a commonly reported feature of PWS. However, published reports relating to pain sensation in PWS are remarkably scarce [15]. Our results show that almost all persons were reported to have high pain thresholds. Examples of this high pain threshold included skinpicking behavior, other forms of self-harm, unrecognized fractures, bruises, burns, blood sampling, all without pain expressions. Serious illnesses such as cholecystitis, appendicitis, pneumonia or erysipelas, were frequently only recognized after some days because symptoms were mild and pain was hardly expressed. Easy bruising has also been anecdotally reported and could, in part, be related to decreased ability to sense pain; no other contributory factors of easy bruising have been identified so far. Therefore, any fever or a refusal to walk (after an injury or fall) should be taken seriously and a good clinical examination and close follow-up are indicated until serious illness or injury has been ruled out. It is important for caregivers to be vigilant for signs of infection and injury that might otherwise be signaled by pain or discomfort. Acute or unexpected changes in behavior, mobility or gait may warrant further investigation [26].

4.5.4. Abnormal temperature regulation

Temperature dysregulation may occur more frequently in individuals with PWS, perhaps related to a defect in thermogenesis [33]. In 66 out of 102 persons in our cohort, parents reported that fever was commonly absent during illnesses and infections. Bouts of fever may be absent during serious illnesses but hyperthermia is also reported in patients without an infectious cause and this may trigger medical investigations. Many parents stated that they do not rely on measuring body temperature during illness in staging the seriousness of illnesses. Physicians should also be careful in attaching to much importance to measuring body temperature in people with PWS.

A proportion of older people with PWS may be at risk of hypothermia. In our study this usually occurred when the outside temperature was cool, or for example after swimming [34]. Episodes of low body temperature were reported in nine persons in our study. This could be related to a diminished capacity for shivering or to the use of psychotropic medication. In view of the relative paucity of published data and the potentially serious nature of this condition, caregivers should be aware of the possible risks. Measurements of basal temperature in the absence of illness could give additional information on the "normal" temperature level in an individual. In persons at risk for hypothermia, a protocol for low body temperature may help to improve care. This protocol should include: when and how to measure the body temperature, how to warm the person up, when to alert a physician and how to prevent hypothermia.

Besides problems in regulating their own body temperature, 75 out of 102 persons in our study experienced problems in assessing temperature of the environment (e.g. estimating bath temperature, problems to adjust the amount and kind of clothes to the weather). This sometimes led to dangerous situations, such as burns caused by hot showers or standing too close to heaters.

5. Conclusion

Using the results of this study, expectations of parents and professionals on the use of medical care utilization by adults with PWS can be adjusted. Especially during emergency situations, in which symptoms are not always clear, it is important to be well informed about the possible health hazards. Information from this cohort may help in preventing conditions and recognizing others in an early stage by developing guidelines to monitor health [19]. Adequate preventive management and treatment of PWS related morbidity, could reduce medical care use in the long term and could improve quality adjusted life years.

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