Deaths in Children with Prader-Willi Syndrome

A Contribution to the Debate about the Safety of Growth Hormone Treatment in Children with PWS

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Key Words

Prader-Willi syndrome, mortality · Obstructive respiratory disorder · Hypoventilation · Sleep apnea · Sudden death

Abstract

Irrespective of GH treatment, children with Prader-Willi syndrome (PWS) suffer more frequently and more seriously from respiratory problems than healthy children. The pathogenesis of such respiratory problems in PWS seems to be multifactorial in origin, but mainly related to insufficiency of respiratory muscles and pharyngeal narrowness. Deaths of children with PWS are reported among GH treated as well as untreated children. Our data show that also disturbed body composition plays an important role in fatal outcomes, possibly enhancing the ventilation disorder. For several years, in our recommendations we have pointed out the secondary risks of increasing obesity. In addition, it is recommended for all children with PWS, in particular before institution of GH therapy, to have polysomnography and an otorhinolaryngologic examination performed, and tonsillectomy in the case of enlarged tonsils. Furthermore, upper airway infections should be treated aggressively.

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Patients with Prader-Willi syndrome (PWS), in addition to disturbed body composition, suffer from numerous medical problems, particularly in relation to respiration. Following two case reports from our group concerning the death of 2 children during growth hormone treatment (GHT) [1, 2] and the subsequently reported sudden death of further children [3, 4], a controversy arose concerning the safety of GHT in children with PWS. In this paper we would like to present currently known facts about the deceased children and develop some hypotheses about mortality in children with PWS.

Data on Deceased Children with PWS without GHT

In very recent publications [5, 6] case reports of children with PWS not treated with GH, who died, were collected through two European and American international searches, based on collaboration with many healthcare professionals and through announcements in journals/meetings/groups of professionals. Moreover, two case reports [7, 8] were published and one further case was reported from Austria [9] (table 1). Of the total of 23 cases below age 18, one child died in an accident; 17 of the remaining 22 died from infections, and 5 of 22 from sleep apnea or hypoventilation and aspiration. Deaths resulting from infections were mostly related to the respiratory tract (n = 11) or to

Table 1. Patients <18 years with PWS who died spontaneously

Patient No.	Country	Death date	Age _{death} years	Sex	GH	Relat. weight, %	BMI kg/m ²	BMI SDS	Cause of death	Autopsy findings	Medical history
1	Japan [13]	1991	0.5	f	none				pneumonia, cardiac decomp.		
2	Estonia [8]	2002	3.5	f	none	>200			bronchitis, cardiac arrest		narcolepsy
3	NL [5]		0	m	none	not obese			prematurity, sepsis	<i>E. coli</i> sepsis	
4	France [5]		0.25	m	none	not obese			hypoventilation	aspiration	
5	Belgium [5]		0.66	f	none	not obese			pneumonia	n.d.	
6	NL [5]		0.83	m	none	not obese			hypoventilation, aspiration	n.d.	
7	USA [5]		1.33	m	none	not obese			sleep apnea, SIDS	SIDS	recurrent pneumonia
8	USA [5]		2	m	none	not obese			sudden resp.fail., pneumonia	pneumonia	
9	NL [5]		2	m	none	not obese			pneumonia, Strep. A	bronchopneumonia	
10	NL [5]		2	f	none	not obese			shock, DIC, gastroenteritis	n.d.	enteritis
11	USA [5]		3	f	none	not obese			accident	n.d.	
12	NL [5]		3	m	none	not obese			SIDS, gastroenteritis	enteritis	enteritis
13	Belgium [5]		3	f	none	not obese			SIDS, early morning unexp.	SIDS	respiratory tract infection
14	USA [5]		3	m	none	not obese			abscess, Strep. A	parapharyngeal abscess	
15	NL [5]		5	f	none	>120			SIDS, resp. tract infection	bronchopneumonia	
16	Belgium [5]		9	m	none	>200			pneumonia, cardiac decomp.	n.d.	
17	USA [6]		0.42	m	none	72	11.8	-3.65	fever, mild pneumonia, SIDS	alveolar infiltrate	failure to thrive
18	USA [6]		0.75	m	none	88	15.5	-1.08	fever, gastroenteritis	enteritis, mild meningitis	
19	Canada [6]		1.58	f	none				fever, resp. tract infection	n.d.	failure to thrive
20	UK [6]		1.67	f	none	70	12.2	-3.61	fever, diarrhea, DIC, unexpected death	alveolar hemorrhage, bronchiolitis	
21	USA [6]		3.5	m	none	154			SIDS, apnea	n.d.	failure to thrive
22	USA [6]		3.5	f	none	137	21.7	5.26	diarrhea (rotavirus), aspiration	aspiration; cerebral malformation	
23	Austria [9]	2002	3.1	m	none	139	22.8	3.7	sudden death, respiratory infection	n.d.	premature 31 weeks laryngotracheo bronchitis
<i>Cases</i>			23	13 m		21	5	5			
<i>Median</i>			2	10 f		6 obese	15.5	-1.08			
<i>Min</i>			0				11.8	-3.65			
<i>Max</i>			9				22.8	5.26			

n.d. = Not done; SIDS = sudden infant death syndrome; DIC = disseminated intravascular coagulopathy.

gastrointestinal disease (n = 5). The clinical course of the respiratory infections in the children was shorter and more acute than anticipated, and death occurred rather suddenly and unexpectedly. Out of 21 children, weight status was known in 19, and only 6 of them were reported to be obese [5, 7–9]; in 15 children, however, no accurate data on weight and height had been provided.

The mortality rate in patients with PWS not treated with GH was recently estimated at 3% per year between age 6 and 56 years compared to 0.13% in the general population below 55 years [10]. Even though mortality rate in children aged 0–5 years was not estimated, more recent reports on causes of death in PWS have predominantly included children younger than 5 years. Therefore, the reported spontaneous death in 22 children up to 5 years of age is most likely far below the actual mortality in this age group. In addition, because PWS has only been

diagnosed in early childhood very recently [11], a substantial number of young children with PWS may have died without having been diagnosed with PWS. Unfortunately, there is no national or international registry recording all patients with PWS who died, whether treated with GH or not.

Data on Deceased Children with PWS Treated with GH and Comparison with Living Controls

Prompted by our case reports on 2 patients who died during GHT [1, 2], Pharmacia/Pfizer searched the KIGS database for similar cases [3]; of a total of 675 children on GHT with documented PWS, three had died (0.44% until fall 2003) [12]. Further cases were found through the Pharmacovigilance databases [12] and case reports as

Table 2. Patients <18 years with PWS who died during GHT

Patient No.	Country	Year of death	Age _{death} years	Sex	GH treatment		Relat. weight %	BMI (Prader) kg/m ²	BMI (Prader) SDS	Cause of death	Autopsy findings	Medical history
					dose mg/kg · w	duration months						
1	Switzerland [2]	1999	0.7	m	0.18	2.5	119	20.2	2.7	sudden death during bottle feeding;	bronchopneumonia	fever; hypoventilation, sleep apnea signs of pulmonary hypertension
2	Switzerland [1]	2000	6.5	m	0.26	5.0	156	23.8	6.6	hypoventilation, sleep apnoea	no autopsy	nocturnal apnea
3	Japan [3] KIGS		15.8	m	0.1	7.0	230	38.0	7.11	acute pneumonia, sudden resp.failure	no autopsy	
4	Spain [3] KIGS	2001	8.0	m	0.15	0.5	206	31.6	10.7	resp. insufficiency, acute bronchitis	respiratory insufficiency	moderate OSA, severe nocturnal hypoventilation
5	USA [3] KIGS	2001	4.7	m	0.24	3.0	212	31.3	14.0	aspiration pneumonia respiratory failure	no autopsy	sleep apnea; non compliant with GH
6	USA [3]		3.0	m	0.12	3.0	210			found dead in bed	pneumonitis	asthma (Salbuterol)
7	Canada [4]	2002	4.0	m	0.16	2.0	262	40.5	20.4	pneumonia	bronchopneumonia subdural hematoma	snoring, benign intracranial hypertension
8	USA [12]	2003	3	f	0.5 mg/d30		somewhat obese			pneumonia	physician waiting for final report	several apiration pneumonias, non-compliant with GH
9	UK [12]		13.0	m		5.0				sudden death, unexplained		
10	UK [12]	2003	14.6	m	0.11	18	254	42.0	8.34	viral URI, resp. failure, severe right heart failure		OSA, chronic heart failure, type 2 diabetes
11	Japan [12]		14	f		48				drowned in the bathtub		
12	Austria [13]	1999	4.9	f	0.24	2.0	127	19.5	3.95	sudden death, cardiorespiratory failure	no autopsy	sleep apnea, CPAP; pulmonalis pressure increase during GH
13	Italy [14]	2003	3.9	m	0.15	7.0	226	28	10.9	sudden death, unexplained	no autopsy	maternal gestational diabetes; slightly abnormal cranial CT
Cases			13		11	13	10	9	9			
Median			4.9		0.16	5.0	211	31.3	8.34			
Min			0.7		0.10	0.5	119	19.5	2.7			
Max			15.8		0.26	48.0	262	42	20.4			
w = Week; OSA = obstructive sleep apnea.												

well as through personal communication [13]. No new cases were reported to KIGS until today [12] (table 2).

Despite major effort including the above-mentioned databases and personal contacts with involved persons and centers caring for patients with PWS, it was not possible to obtain more information than provided in this paper.

Respiration

As shown in table 2, 10 of 13 children died in the context of respiratory insufficiency; respiratory problems were documented in 9 of these 10 children before they started GHT.

Table 3. Controls matched to deceased children with PWS documented in table 2 for 1. duration of GHT, 2. age, 3. sex

Patients No. tab.2	initial	Age _{death} years	Sex	GH treatment		Rel. weight %	BMI (Prader) kg/m ²	BMI (Prader) SDS
				dose mg/kg·week	duration months			
ad 1	MZ	0.65	m	0.29	3	98	16.1	−0.45
ad 2	PS	7	f	0.29	6	121	18.7	2.99
ad 3	no patient found to match the pubertal patient during 7 months of GHT							
ad 4	AM	7.6	f	0.33	6	99	15.1	−0.27
ad 5	HR	4.7	f	0.30	3	115	17.5	1.64
ad 6	GD	3.5	m	0.23	3	116	17.5	1.81
ad 7	ES	4.3	m	0.33	3	93	14.0	−1.04
ad 8	MG	2.95	m	0.30	31.5	110	17	1.24
ad 9	MS	13.2	f	0.40	6	109	17.3	−0.19
ad 10	SM	14.8	f	0.25	17	123	20.3	0.52
ad 11	MA	14.05	f	0.20	60	126	23.7	2.88
ad 12	CD	5.3	f	0.26	2	124	18.9	3.27
ad 13	PB	3.6	m	0.38	7	90	14.1	−0.93
<i>Cases</i>		<i>11</i>		<i>11</i>	<i>11</i>	<i>11</i>	<i>11</i>	<i>11</i>
Median		5.30		0.29	6.00	115	17.50	1.24
Min		0.65		0.20	2.00	93	14.00	−1.04
Max		14.80		0.40	60.00	126	23.70	3.27

Duration of GHT

It was seen that GHT duration in 10 of the deceased children amounted to a maximum of 7 months; most children died during the first 3 months of therapy. The 3 remaining children who had been treated with GH for a longer time had suffered from particular additional problems: #8 was noncompliant with GHT, #10 had morbid obesity with obstructive sleep apnea and heart failure and #11 drowned in the bathtub.

Weight Indices

In 9 with sufficient data on weight of 13 deceased patients, BMI and BMI SDS could be calculated, 11 were described to be ‘obese’. For comparison purposes, we matched every deceased child with a child of our current study using the following criteria: (1) duration of therapy; (2) age, and (3) sex (table 3). If more than one candidate was found, the mean of the suitable children was used. It was found that the deceased children were markedly more obese than the controls from our study, and the GH dose was similar or even lower in the deceased children.

In a second attempt to compare the weight of the deceased children with controls we compared the weight indices of the two deceased children from our own study with all other children of the same age groups of our study (table 4). The first child died at the age of 7 months, 2.5

Table 4. Comparison between the weight indices of the 2 deceased children from our own study with all other children of the same age groups of our study

After 3 months GHT	Patient 1	Control group 1, n = 10 median (range)
Age, years	0.7	0.9 (0.6–1.4)
Relative weight, %	119	88.2 (70.6–100.0)
BMI, kg/m ²	20.2	14.9 (12.1–17.0)
BMI SDS	2.7	−1.52 (−3.73–0.01)
WFH SDS	2.34	−1.55 (−3.78–0.09)
After 6 months GHT	Patient 2	Control group 2, n = 9 median (range)
Age, years	6.5	7.3 (4.3–10.1)
Relative weight, %	156	114.0 (100.5–136.8)
BMI, kg/m ²	23.8	17.2 (15.1–20.7)
BMI SDS	6.6	1.30 (−0.28–4.18)
WFH SDS	7.38	1.90 (−0.05–4.7)

months after the institution of GHT. As controls, we chose any child of our study who was between 0 and 1.5 years old and had at that time been treated for 3 months with GH (table 4). The second child died at the age of 6.5 years, 5 months after the institution of GHT. As controls we used

any child between 4 and 10 years old who had at that time been treated during 6 months with GH. It turned out that the 2 deceased children of our study were far more obese than all other children of the same age group of our study. The very young patient No. 1 was not only the most obese of his age group, but his weight for height (WfH) SDS increased more than in all other very young patients during the first 3 months of GHT (WfH 0.6 SD at onset of GHT to 2.34 SD some days before he died). The older patient, patient No. 2, was not only the most obese of his age group but also the only in his group who failed to reduce weight and fat mass (WfH SDS 7.3 at onset of GHT and 7.4 after 5 months, 1 month before he died).

Pathophysiological Considerations

The pathogenesis of the respiratory problems in PWS seems to be multifactorial in origin, including peripheral and central mechanisms. In some patients [1, 2, 14], primary disturbance of respiratory control with abnormally low response to high $p\text{CO}_2$ and/or to low $p\text{O}_2$ is present already at birth [15]. Sleep apnea is found in 50–100% of children with PWS leading to alveolar hypoventilation [16]. Irrespective of GHT, children with PWS [1–8] seem to suffer more frequently and from more serious respiratory problems with or without infections than healthy children.

From the data in tables 1 and 2, several pathophysiological explanations may be deduced.

Reduced Diameter of the Upper Airways

Airway obstruction is caused by pharyngeal muscular hypotonia, facial dysmorphisms (e.g. retrognathia) and/or tonsillar hyperplasia. Radiological studies of persons with PWS have shown below-average cross-sectional area at the oropharyngeal or nasopharyngeal level [17]. Hyperplastic tonsils in children with PWS and tonsillar infection may further lead to upper airway obstruction. In addition, increased fat depots may also reduce throat diameter.

In fact, we were informed by parents that their children usually sleep with a hyper-extended neck, which can be interpreted as an attempt to optimize the diameter of the throat and of the upper airways, respectively (fig. 1).

Ventilatory Restriction

The disturbed body composition in PWS, documented from infancy on, might be an important factor for impaired respiration [18, 19], especially the decrease in the

Fig. 1. Neck overextension during sleep in 2 children with PWS indicating the reflex to counteract upper airway obstruction. Informed consent for publication of the photos was obtained from the parents.

mass of the respiratory muscles. The hypothesis that body composition and respiratory muscles are involved in respiratory insufficiency in PWS is supported in studies in children and adults with PWS [16, 20, 21]. The restrictive ventilatory impairment is exacerbated by increased fat depots and possibly aggravated in some cases by kyphoscoliosis.

Disturbances in Respiratory Regulation

Hypoventilation as a consequence of both mechanisms causes a chronic elevation of $p\text{CO}_2$, which further aggravates the situation because of an increase of the respiratory drive set-point in the brain stem. [14, 16, 22].

Respiratory Infections

Hypoventilation with insufficient air flow also leads to increased infect susceptibility. Thus, about half of the

children not treated with GH (table 1), as well as at least 7 of 13 of those children who died while on GHT (table 2), had shown signs of respiratory tract infection. This further aggravated the existing respiratory insufficiency and thus contributed to their death.

Pulmonary Hypertension

Alveolar hypoventilation also causes pulmonary vascular obstruction with a pulmonary hypertension and finally cor pulmonale [16]. Signs of a slight pulmonary hypertension were detected in 3 of the children with PWS treated with GH (table 2, patient #1, by electrocardiography, and by echocardiography in patients #2 and #12, the latter died after a documented increase in pulmonary pressure during GHT [13]).

Possible Impact of GHT on Respiration and Mortality

As Carrel et al. [22], Lindgren et al. [23] and Haqq et al. [17] showed, the beneficial effects of GHT on growth and body composition are accompanied by an improvement in respiratory function and an increase in CO₂ sensitivity. In this context, higher muscle mass and decreased fat mass may improve alveolar ventilation by reducing alveolar pCO₂ and thus interrupting the vicious circle through an increased CO₂ sensitivity in the brain stem. It is, however, important to note that these studies showed a beneficial effect on respiration as early as after 6 months of therapy.

The following observations underline that GHT influences mortality in children with PWS:

Duration of GHT

In general, most of the children with PWS were started with GHT 4 years ago, when in 2000, GH was admitted for therapy in PWS, or even earlier in trials with GHT starting in 1992. However, in this context, it is surprising that most children complying with GHT died during the first months on GHT, but not later, except those with preceding heart failure. It may be deduced that GHT increases mortality during the first 7 months of treatment and decreases mortality thereafter, as supported by the data in table 2. In fact, as quoted above, GHT was shown to improve respiratory function after 6 months and, thus, could provide some protection against hypoventilation [16, 21, 22].

It is nevertheless also conceivable that GHT additionally increases the risk of respiratory insufficiency during

the first few months of treatment: First, in those patients with pre-existing distinctively impaired respiration, GH might augment volume load, because GHT is known to normalize previously decreased hydration during the first few weeks. Second, a tonsillar hyperplasia can be augmented by GHT, and increases the airway obstruction [24, 25].

Obesity

It is striking that most children who died without having received GHT were reported not to have been obese, while those children who died during GHT were more obese than the controls. In addition, our own 2 patients who died differed from our other patients [26], inasmuch as they did not normalize fat mass during GHT. As deduced from longitudinal observation in these 2 patients, the pre-existing and persisting obesity may have further aggravated their respiratory problem. Therefore, data on deceased children with PWS should be analyzed, not only with regard to the level of obesity before the institution of GHT, but also regarding the progression of obesity after the initiation of GHT, since it represents a risk factor for respiratory failure or sudden death. Unfortunately, longitudinal data on other deceased children could not be obtained.

The observation that the children who died spontaneously were younger than the children during GHT, median 2 vs. 4 years, may be due to a recruiting bias. Up to now, only a few children under 2 years of age are being treated with GH because this age group is only treated in studies in a small number of centers.

Conclusions

In general, infants with PWS already suffer from hypoventilation. Hypoventilation is probably the consequence of insufficient respiratory muscles, some pharyngeal narrowness and the development of decreased CO₂ sensitivity. Obesity plays an important role in fatal outcomes, possibly enhancing the ventilation disorder, as does kyphoscoliosis. Hypoventilation further leads to a higher susceptibility to infections, which in its own right may aggravate respiratory insufficiency. We consider that in most if not all patients who died during GHT, a combination of extreme obesity and pre-existing ventilation disorder might not have been given the attention it merited. We hypothesize that all of these children had hypoventilation with impaired respiratory regulation even before GHT was begun.

Recommendations

For several years, we have pointed out the secondary risks of increasing obesity during GHT (www.childgrowth.org). In addition to vigorous weight control by parents and caregivers, we have introduced the following precautionary measures in our outpatient clinic: Before we start with GHT, we perform polysomnography and an otorhinolaryngologic examination and have the patients undergo tonsillectomy if necessary. The parents should find out whether the child snores and should inform us immediately if snoring augments or begins, and also if there are signs of upper airway infections. In this context, in May 2003, Pfizer, the pharmaceutical company which is manufacturing and selling recombinant GH in the specific

indication of PWS, has released a warning on the use of GH in patients with PWS and severe obesity or severe respiratory impairment. They recommended evaluating every child with PWS and GHT as mentioned above.

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