ORIGINAL ARTICLE

Sudden Unexpected Death During Sleep in Familial Dysautonomia: A Case–Control Study

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Study Objectives: Sudden unexpected death during sleep (SUDS) is the most common cause of death in patients with familial dysautonomia (FD), an autosomal recessive disease characterized by sensory and autonomic dysfunction. It remains unknown what causes SUDS in these patients and who is at highest risk. We tested the hypothesis that SUDS in FD is linked to sleep-disordered breathing.

Methods: We retrospectively identified patients with FD who died suddenly and unexpectedly during sleep and had undergone polysomnography within the 18-month period before death. For each case, we sampled one age-matched surviving subject with FD that had also undergone polysomnography within the 18-month period before study. Data on polysomnography, EKG, ambulatory blood pressure monitoring, arterial blood gases, blood count, and metabolic panel were analyzed.

Results: Thirty-two deceased cases and 31 surviving controls were included. Autopsy was available in six cases. Compared with controls, participants with SUDS were more likely to be receiving treatment with fludrocortisone (odds ratio [OR]; 95% confidence interval) (OR 29.7; 4.1–213.4), have untreated obstructive sleep apnea (OR 17.4; 1.5–193), and plasma potassium levels <4 mEq/L (OR 19.5; 2.36–161) but less likely to use noninvasive ventilation at night (OR 0.19; 0.06–0.61).

Conclusions: Initiation of noninvasive ventilation when required and discontinuation of fludrocortisone treatment may reduce the high incidence rate of SUDS in patients with FD. Our findings contribute to the understanding of the link between autonomic, cardiovascular, and respiratory risk factors in SUDS.

Keywords: autonomic nervous system, hereditary sensory and autonomic neuropathy, hypokalemia, sleep apnea, noninvasive ventilation.

Statement of Significance

Sudden unexpected death during sleep (SUDS) is the most common cause of death in patients with familial dysautonomia (FD), although, until now, it was unknown who was at highest risk. This case–control study including polysomnography and arterial blood gases data shows that the presence of untreated obstructive sleep apnea, fludrocortisone treatment, and potassium levels in the low range of normality were independently associated with increased risk for sudden death during sleep in FD. In contrast, treatment with noninvasive ventilation at night was independently linked with reduced risk for SUDS. Initiation of noninvasive ventilation when required and discontinuation of fludrocortisone treatment may reduce the high incidence rate of SUDS in FD.

INTRODUCTION

Sudden unexpected death during sleep (SUDS) is the most common cause of death in patients with familial dysautonomia (FD, Riley–Day syndrome, hereditary sensory, and autonomic neuropathy type III), a rare autosomal recessive disorder first described in 1949 in children of Jewish Ashkenazi ancestry.[1,2] The disease is due to a founder mutation in the IkB kinase-associated protein gene (*IKBKAP*)[3–5] causing impaired development of sensory and afferent autonomic nerves.[6] Hallmarks of FD include impaired pain and temperature sensation, absent deep tendon reflexes, gait ataxia,[7] chronic lung disease,[8] and afferent baroreflex failure leading to orthostatic hypotension and paroxysmal hypertension,[9,10] all which contribute to morbidity and mortality.[2,11]

It remains unknown what causes SUDS in FD patients and who is at highest risk. One of the potential risk factors for SUDS is sleep-disordered breathing, present in most patients with FD.[12–14] Ventilatory responses to hypercapnia are reduced and to hypoxia are almost absent in all FD patients. Thus, in response to hypoxia, patients develop paradoxical hypotension, hypoventilation, bradycardia, and potentially, death.[12,15–18]

We hypothesized that the high incidence of SUDS in patients with FD might be linked to respiratory abnormalities during sleep. To test this hypothesis, we analyzed the clinical features and polysomnography findings of patients with FD who died suddenly during sleep and compared them to age- and gender-matched FD patients who remained alive at the time of the study. To expand our results, we also included data from electrocardiograms, arterial blood gases, and blood metabolic panels obtained during daytime.

METHODS

Study Design

We conducted a case–control study of patients with genetically confirmed FD. Cases were defined as patients with FD who died suddenly and unexpectedly during sleep. Controls were defined as patients with FD who remained alive at the time of the study. Cases and controls were drawn from the New York University (NYU) FD Registry. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for case–control studies.[19]

NYU FD Dysautonomia Registry

The NYU FD Registry is an ongoing, prospective registry of patients FD. The Registry started in 1970 and contains clinical and diagnostic data, including cause of death, on 670 patients at the time of the study. Of these, 327 (49%) remained alive at the time of the study. All patients have genetically confirmed FD; more than 99% are homozygous for the same mutation (6T>C change) in the *IKBKAP* gene. The majority of patients included in the Registry (52%) are from the United States. The remaining patients are from Israel, Canada, United Kingdom, South America, South Africa, Australia, and Belgium. Patients are followed closely and seen at least once a year.

Cases

Of all patients included in the NYU FD Registry during a 45-year period (1970–2015), we first extracted those individuals in whom SUDS was listed as the cause of death. SUDS was defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death occurring during sleep, with or without evidence of a seizure. Cases in which postmortem examinations were not performed—and therefore no toxicological or anatomical cause of death could be ruled out—were classified as "probable SUDS."[20] Patients with signs or symptoms of respiratory infection or fever at the time of death were excluded. Of all patients with probable SUDS, we then selected those who had a full hospital polysomnography performed in a period no longer than 18-months before death.

Controls

For each case of SUDS, we selected one age-matched control patient (age at the time of death). Controls were patients with FD included in the NYU FD Registry that were alive at the time of study and had undergone a polysomnography within the 18-month period before this study.

Data Collection

The following test results (continuous data) were obtained: Polysomnography variables comprised the apnea-hypopnea index (AHI) including obstructive and central apneas, the minimal (nadir) oxygen saturation during sleep, and the time of sleep with an oxygen saturation below 90%. Because all patients also had electrocardiogram (EKG), metabolic panel, complete blood count, and arterial blood gases performed in the same time period, the following parameters were extracted: heart rate, QRS interval, QTc interval, PR interval, hemoglobin, hematocrit, glucose, electrolytes, creatinine, blood urea nitrogen, pO_2, pCO_2, HCO_3, and pH. The vast majority of participants also had ambulatory blood pressure (BP) monitoring, in which BP readings are recorded every 30 minutes during 24 hours;[21] we obtained the standard deviation of the systolic BP, as a marker of cardiovascular autonomic variability.[22] The dosages of the most frequent medications taken by these patients (fludrocortisone, midodrine, benzodiazepines, and clonidine) were also included in the analysis.

The following clinical (categorical) data were obtained: presence of obstructive sleep apnea (OSA; defined as an AHI >5 events/hour); history of epileptic, hypoxic, or febrile seizures; presence of active epilepsy (defined as participants who were currently taking medication to control epilepsy, or had one or more epileptic seizures in the past year, or both); cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, stroke/transient ischemic attack) and heart disease (ischemic, valvular, or congenital/inherited heart disease and cardiac arrhythmia); presence of pacemaker; treatment history (midodrine, fludrocortisone, clonidine, benzodiazepines); and use of noninvasive ventilation such as continuous positive airway pressure or bilevel positive airway pressure. Because most patients with FD undergo Nissen fundoplication surgery and percutaneous gastrostomy tube placement for the management of vomiting episodes and neurogenic dysphagia, these were also included in the analysis. The frequency of nocturnal feedings (via the gastrostomy tube) was also analyzed.

We made an effort to collect information on the circumstances of death by exhaustive medical record review, coroner's office report, or by formal interview with the bereaved relatives.

Autopsy findings were also documented, although postmortem examinations are seldom performed in this population due to religious reasons.

Table 1—Characteristics of Cases With Sudden Unexpected Death During Sleep (n = 32).

Characteristics	No (%)
Women	14 (44)
Age	
0–10	2 (6)
11–17	7 (22)
18–30	9 (28)
31–50	14 (44)
>51	0 (0)
History of seizures	26 (81)
Epileptic	11 (34)
Hypoxic	10 (31)
Hyponatremic	5 (16)
Febrile	1 (3)
Active epilepsy	5 (16)
Cardiac disease[#]	6 (19)
Pacemaker	6 (19)
Stroke/transient ischemic attack	0 (0)
Diabetes mellitus	0 (0)
Treatments	
Benzodiazepines	24 (75)
Fludrocortisone	24 (75)
<0.1 mg/day	0
0.1–0.15 mg/day	7 (22)
0.2–0.3 mg/day	16 (50)
>0.3 mg/day	1 (3)
Clonidine	12 (38)
Midodrine	10 (31)
Fludrocortisone and midodrine	12 (38)
Beta-blockers	1 (3)
Noninvasive ventilation at night[$]	3 (9)
Autopsy	6 (19)

[#]Cardiac disease includes ischemic, vascular, congenital/inherited disease, atrial fibrillation, and third-degree atrioventricular block.
[$]Noninvasive ventilation at night includes continuous positive air pressure (CPAP) and bilevel positive airway pressure.

Table 2—Comparison of Continuous Characteristics in Cases and Controls.

Characteristic	Cases (*n* = 32)		Controls (*n* = 31)		*p*-value
	Mean (SD)	Range	Mean (SD)	Range	
Age, year	29.2 (12.5)	9–50	28.9 (11.7)	9–54	.99
Body mass index, kg/m^2	17.9 (2.8)	13.7–23.9	17.2 (2.1)	14.4–22.2	.81
Polysomnography					
Total sleep time, minutes	392 (145)	181–491	404 (101)	214–523	.78
REM latency, minutes	110 (59)	0–308	119 (61)	16–321	.81
Arousal index, events/hour	28.1 (16.1)	1.2–52.5	24.9 (18)	2–74.4	.38
Stage 1 sleep, %	7.5 (4.5)	1.8–24	5.28 (4.1)	0–17	.19
Stage 2 sleep, %	50.7 (13.2)	35.5–79.2	48.7 (25.1)	0–79	.55
Stage 3 sleep, %	19.1 (12.9)	0–38.3	25.1 (12.5)	0–90	.42
REM sleep, %	19.0 (11.4)	0–20.5	20.6 (10.1)	8.6–44	.63
Apnea-hypopnea index, events/hour	16.7 (14.4)	0–59.3	6.7 (4.2)	0–23.4	.007*
Apnea-hypopnea average duration, seconds	29.8 (7.2)	0–38	22.2 (11.8)	0–40	.73
Minimal O_2 saturation, %	69 (18.9)	30–97	81 (8.4)	65–93	.029*
Total sleep time with SpO_2 <90%, %	9.1 (15.4)	0.1–95	2.3 (4.1)	0–16.8	.014*
EKG					
Heart rate, bpm	83.5 (10)	68–107	82.5 (12)	59–105	.71
QRS interval, ms	80.6 (17.9)	48–100	89.2 (21.8)	50–160	.06
QT interval, ms	345 (27)	300–388	360 (42)	284–460	.38
QTc interval, ms	404 (11)	380–427	419 (29)	375–482	.12
PR interval, ms	121 (26)	80–160	133 (18)	96–162	.07
Standard deviation of 24-hour systolic blood pressure, mmHg	24.1 (6.5)	17.3–31	23.1 (5.1)	14.2–29.9	.60
Arterial blood gases					
pH	7.41 (0.05)	7.34–7.51	7.40 (0.03)	7.33–7.46	.27
pO_2, mmHg	78.5 (14.2)	52.5–107	83.5 (17.8)	50–105	.16
pCO_2, mmHg	42.1 (7.65)	23–59	44.3 (5.8)	35–64	.25
$pHCO_3$, mEq/L	25.1 (4.6)	15–31.1	27.3 (2.6)	24.3–35.6	.18
Hematological parameters					
White blood cell count, ×10^9/L	7.55 (3.54)	4.3–10.2	7.32 (2.35)	4–13.7	.92
Red blood cell count, ×10^9/L	4.26 (0.47)	3.3–5.5	4.11 (0.6)	2.7–5.1	.40
Hemoglobin, mg/dl	12.75 (1.29)	10.3–15.2	15.68 (20.53)	9.8–14.8	.43
Hematocrit, %	37.61 (4.11)	29.8–46.6	36.41 (4.37)	26.7–44.3	.33
Metabolic parameters					
Sodium, mEq/L	140 (4.3)	134–147	139 (3.3)	132–144	.31
Potassium, mEq/L	4.3 (0.6)	3.3–6.2	4.7 (0.5)	4.1–5.9	<.0001*
Chloride, mEq/L	102 (4.3)	88–109	100 (3.9)	91–107	.20
Creatinine, mg/dL	1 (0.43)	0.3–2.4	1.05 (1.08)	0.4–1.6	.43
Blood urea nitrogen, mg/dL	23.3 (9.5)	3–40	24.1 (11.5)	13–38	.51

Table 2—*Continued*

Characteristic	Cases (n = 32)		Controls (n = 31)		p-value
	Mean (SD)	Range	Mean (SD)	Range	
Medications					
Fludrocortisone, mg/day	0.14 (0.10)	0–0.4	0.02 (0.04)	0–0.1	<.0001*
Midodrine, mg/day	3 (4.7)	0–17.5	3.3 (4.9)	0–15	.66
Benzodiazepines, mg/day	4.8 (4.7)	0–17.5	4.9 (4.6)	0–16	.78
Clonidine, mg/day	0.04 (0.07)	0–0.2	0.06 (0.06)	0–0.2	.41

*Statistically significant differences.
REM = rapid eye movement; SD = standard deviation.

Statistical Analysis

Patient and event characteristics were described and compared between cases and controls using χ^2 statistics (Pearson/Fisher exact test where appropriate) for categorical data and the Student t test/Mann–Whitney U test for quantitative continuous data. Missing quantitative data were handled with multiple imputation methods. If significant differences were found, these quantitative variables were transformed into categorical ones. Then, to identify categorical risk factors for SUDS (cases vs. controls), univariable and multivariable conditional logistic regression was employed, thereby accounting for matched data. The interaction term "with/without noninvasive ventilation" was used in the multivariable analysis when accounting for the risk factor OSA. p-Values <.05 were considered significant. The annual incidence rate was calculated according the formula $d/y \times 10{,}000$, where d is the number of SUDS cases and y is the number of people at risk (number of subjects × observation period). Analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, USA).

Protocol Approval and Patient Consents

The Institutional Review Board of the NYU School of Medicine approved the NYU FD Registry. Written informed consent was obtained from all FD patients (or their guardians when appropriate) at the time of enrolment in the Registry.

RESULTS

Cases and Controls

At the time of study, 669 patients with FD had been included in the NYU FD Registry. Of these, 343 (51%) had deceased. Of the deceased, 108 (31%) fulfilled criteria for probable SUDS. Therefore, the incidence rate of SUDS in FD is 3.4 per 1000 person-year. Of the 108 patients fulfilling criteria for probable SUDS, 32 (14 women) had undergone polysomnography in the 18-month period before death and were included in the final analysis (Table 1). SUDS occurred most frequently during the second and third decades of life (mean age at death was 29.3 ± 12.4 years old).

Detailed circumstances of death were documented in 25 cases. Subjects were found dead at night (between 01.00 am and 05.00 am) in 14 cases, in the morning (between 08.00 am and 12.00 pm) in six cases, and in the afternoon or evening (between 05.00 pm and 11.00 pm) in five cases. All cases were presumed to be sleeping at the time of death. All cases (except one who was found sitting upright after a long car travel) were found lying in bed (15 in the supine position, seven in the prone position and two lying on their side). None was found partially or completely fallen off the bed. None of the cases were found with their head bent forward or other position suggesting compromised breathing. In none of the cases gagging or choking sounds were identified around the event. None of the cases had their tongue or lips bitten although there was urinary incontinence in one case.

Postmortem studies were available in six cases. All of them showed brainstem, spinal cord, and dorsal root ganglia atrophy, which are pathological hallmarks of familial dysautonomia.[23,24] These six cases showed no structural cardiac pathology and no structural brain lesions. Most of them had nonspecific pulmonary congestion or focal hemorrhage. These patients were therefore classified as definite SUDS (Supplementary Table 1).

We included 31 age-matched surviving patients (15 women) with a recent polysomnography as controls.

Characteristics of Cases and Controls

Characteristics were analyzed in the 32 cases and 31 controls. AHI (p = .007) and the total sleep time spent with oxygen saturation below 90% were higher in cases than in controls (p = .014). In all cases and controls, apneas and hypopneas were predominantly obstructive. Minimum oxygen saturation during sleep (p = .029) and plasma potassium levels (p<.0001) were lower in cases than in controls. No patient had hypokalemia (<3.5 mEq/L) or hyperkalemia (>5.5 mEq/L). Cases were receiving a higher daily dose of fludrocortisone than controls (p<.0001). There were no differences in the EKG, arterial blood gases, BP variability, or complete blood count results (Table 2).

To further understand the relationship between fludrocortisone and plasma potassium levels, we performed a linear regression including both cases and controls, finding that higher fludrocortisone daily dosage was associated with lower plasma potassium levels (r^2 = 0.19; p = .0005).

The prevalence of seizures of any kind, epileptic seizures, and the use of fludrocortisone was higher in cases than in controls. Conversely, the use of noninvasive ventilation was lower in cases than in controls. In multivariable analysis, of these,

Table 3—Comparison of Categorical Characteristics in Cases and Controls.

Characteristic	Cases (*n* = 32)	Controls (*n* = 31)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Women, *n* (%)	14 (44)	15 (48)	0.82 (0.39–2.23)	0.16 (0.21–1.80)
History of seizures, *n* (%)	26 (81)	14 (45)	5.26 (1.69–16.3)*	1.19 (0–50)
Epileptic	11 (34)	3 (10)	4.88 (1.21–19.7)*	1.26 (0–50)
Hypoxic	10 (31)	7 (23)	1.56 (0.50–4.80)	1.22 (0–50)
Hyponatremic	5 (16)	3 (10)	1.72 (0.38–7.95)	1.76 (0–50)
Febrile	1 (3)	1 (3)	0.97 (0.05–16.2)	9.21 (0–50)
Active epilepsy, *n* (%)	5 (16)	3 (10)	1.72 (0.38–7.95)	1.74 (0–50)
Cardiac disease[#], *n* (%)	6 (19)	6 (19)	0.96 (0.27–3.38)	0.36 (0.07–17)
Pacemaker, *n* (%)	6 (19)	7 (23)	0.80 (0.23–2.69)	0.25 (0.05–12)
Stroke/TIA, *n* (%)	0 (0)	0 (0)	0.96 (0.01–50)	—
Diabetes mellitus, *n* (%)	0 (0)	0 (0)	0.96 (0.01–50)	—
Treatments, *n* (%)				
Benzodiazepines	24 (75)	27 (87)	0.44 (0.12–1.67)	1.4 (0.14–13.5)
Fludrocortisone	22 (69)	6 (19)	9.17 (2.9–29.34)*	29.7 (4.1–213.4)*
Clonidine	12 (38)	19 (61)	0.38 (0.14–1.04)	0.53 (0.18–3.3)
Midodrine	10 (31)	13 (42)	0.63 (0.22–1.77)	0.07 (0.01–1.22)
Beta-blockers	1 (3)	2 (6)	0.47 (0.04–5.44)	0.02 (0.01–14)
Potassium supplements	6 (19)	8 (25)	0.66 (0.18–2.02)	0.71 (0.18–3.11)
Noninvasive ventilation at night[$]	3 (9)	12 (39)	0.18 (0.04–0.72)*	0.19 (0.06–0.61)*
Obstructive sleep apnea[&], *n* (%)	18 (56)	9 (29)	2.93 (1.04–8.25)*	17.4 (1.5–193.6)*
With noninvasive ventilation	3 (9)	3 (10)	—	0.96 (0.21–4.4)
Without noninvasive ventilation	15 (47)	6 (19)	—	3.67 (1.26–12.16)*
Minimum sleep $SatO_2$ ≤ 88%, *n* (%)	22 (69)	16 (51)	1.27 (0.47–3.41)	0.32 (0.03–3.58)
Potassium ≤ 4 mEq/L, *n* (%)	13 (41)	1 (3)	19.5 (2.36–161)*	33.4 (1.8–619.3)*
Nissen fundoplication, *n* (%)	25 (78)	28 (80)	0.38 (0.10–1.69)	0.51 (0.21–2.11)
Percutaneous gastrostomy tube, *n* (%)	25 (78)	28 (80)	0.38 (0.10–1.69)	0.51 (0.21–2.11)
Nocturnal feedings, *n* (%)	8 (25)	12 (39)	0.52 (0.19–1.47)	0.33 (0.14–4.21)

*Significant associations.
[#]Ischemic, vascular, and congenital/inherited disease, atrial fibrillation, and third-degree atrioventricular block.
[$]Includes continuous positive air pressure (CPAP) and bilevel positive airway pressure.
[&]Defined as an apnea-hypopnea index >5 events/hour.
CI = confidence interval; OR = odds ratio; TIA = transient ischemic attack.

only fludrocortisone treatment (odds ratio [OR] 29.7; 95% confidence interval [CI]: 4.1–213.4), OSA (OR 17.4; 95% CI: 1.5–193.61) and potassium levels < 4 mEq/L (OR 33.4; 95% CI: 1.8–619.3) were independently associated with SUDS in FD patients, whereas the use of noninvasive ventilation at night (OR 0.19; 95% CI: 0.06–0.61) was a protective factor against SUDS (Table 3). When the interaction term "with or without noninvasive ventilation" was introduced in the multivariable analysis, untreated OSA was independently associated with SUDS (OR: 3.67; 95% CI: 1.26–12.16). There were no differences in the frequency of cardiac disease, Nissen fundoplication, percutaneous gastrostomy tube, or nocturnal feedings.

DISCUSSION

This is the first study analyzing possible risk factors associated with SUDS in patients with FD. Treatment with fludrocortisone, plasma potassium levels <4 mEq/L, and untreated OSA were independently associated with a greater likelihood of SUDS. Conversely, treatment with nocturnal noninvasive ventilation was associated with a reduced likelihood of SUDS.

Fludrocortisone (9α-fluorocortisol) is a synthetic mineralocorticoid that increases renal sodium and water reabsorption, expands intravascular volume, and increases BP. Treatment with fludrocortisone for orthostatic hypotension in patients with FD became widespread in the 1990s, sometimes at very high

dosages (up to 0.4 mg/day). Hypokalemia is a frequent side effect.[25] Long-term use of fludrocortisone in FD exacerbates supine hypertension and accelerates renal damage.[22] Creatinine and blood urea nitrogen levels were similar between cases and controls; it is reasonable to assume that lower serum potassium levels in cases with SUDS were the result of fludrocortisone treatment. Supporting this assumption, a linear regression showed that higher daily dosages of fludrocortisone were associated with lower plasma potassium levels. Cases and controls had similar degree of cardiovascular dysautonomia (as measured by ambulatory BP monitoring), indicating that the high frequency of fludrocortisone treatment in the cases was not an epiphenomenon of more severe cardiovascular autonomic dysfunction.

In the general population, hypokalemia and plasma potassium levels in the lower range of normality are independent risk factors for life-threatening arrhythmias and sudden cardiac death.[26] Interestingly, all drugs proven to reduce mortality and morbidity rates in patients with cardiovascular disease increase plasma potassium concentration.[26]

OSA is also a well-known risk factor for sudden cardiac death in the general population.[27,28] The repetitive apneas and subsequent hypoxemia result in cardiac autonomic abnormalities leading to arrhythmias and death.[29] Cardiac autonomic changes induced by sleep-disordered breathing are reversible by noninvasive ventilation with continuous positive airway pressure,[30,31] which could potentially prevent sudden cardiac death. Our findings of reduced risk of SUDS in FD patients being treated with noninvasive ventilation are consistent with this. Moreover, in patients with FD, failure to receive inputs from peripheral chemoreceptors, carried by the IX (glossopharyngeal) and X (vagus) cranial nerves to the central nervous system, results in markedly blunted ventilatory responses to hypoxia. Ventilatory responses to hypercapnia are reduced but still present. Also, there is no compensatory increase in sympathetic outflow in response to hypoxia; instead, in FD patients, hypoxia results in bradycardia and hypotension.[15,16,18] We found no evidence that epileptic seizures played a role in the pathogenesis of SUDS in FD. The presence of active epilepsy was similar in cases and controls, and the circumstances surrounding death were not indicative of seizures, except for one case with urinary incontinence.

Therefore, SUDS in FD seems to result from a combination of respiratory and cardiac dysfunction, namely: (1) cardiac autonomic dysfunction in the setting of baroreflex failure aggravated by sleep-disordered breathing, (2) hypoxia-induced bradycardia, and (3) increased propensity toward arrhythmogenesis induced or aggravated by low plasma potassium levels.

The incidence of SUDS in FD patients is one of the highest reported in any disorder. The annual incidence rate of SUDS in patients with FD is 3.4 per 1000 person-year, compared to 0.5–1 per 1000 person-year of sudden unexpected death in epilepsy.[32] This high incidence is probably due to the unfortunate combination of sleep-disordered breathing and cardiac autonomic dysfunction. The interaction between cardiovascular autonomic and sleep dysfunctions also underlies the pathogenesis of SUDS in other conditions such as multiple system atrophy,[33] congenital central hypoventilation syndrome,[34] and long-QT syndrome.[35] In our patients with FD, in addition, treatment with fludrocortisone leading to low plasma potassium concentrations likely increased the risk further.

A major strength of our study is that we included only cases with probable or definite SUDS. This is more specific than previous studies that included all types of death (eg, pneumonia). Autopsy confirmation was only available in six cases, all of them showing no cardiac or brain structural abnormalities that could explain the death. In keeping with this, our study did not find any association between increased likelihood of SUDS and previous cardiac disease or decreased likelihood of SUDS and cardiac pacemaker implantation. This is consistent with a previous study showing that pacemakers might decrease the incidence of bradyarrhythmias but did not prevent sudden death in patients with FD.[36] Another study found that increased QT variability was associated with all-cause death in FD, although this finding was probably due to ventilatory problems, such as sleep-disordered breathing, rather than to a primary arrhythmia.[37] Five of our six cases with pathological confirmation had nonspecific pulmonary congestion with no specific signs of infection or disease. Pulmonary congestion and edema is a common and nonspecific phenomenon that may develop either as a consequence of hypoxia or a few hours after death as a time-dependent change due to pressure gradient between pulmonary vasculature and the alveolar spaces and an alteration of capillary permeability.[38]

Another potential limitation in our study is that we only selected one matched-control per case. Because we wanted to focus on sleep-related risk factors, we required all subjects to have a polysomnography performed recently. Inclusion of additional controls with incomplete information on sleep parameters would have resulted in biased results.

Patients with FD were recommended to have a polysomnography at their annual visits at our center, regardless of the presence of symptoms of sleep-disordered breathing. In keeping with this, the percentage of patients with a polysomnography in the deceased patients group was similar to the percentage in the surviving patients group (~10% in both cases). However, as the percentage in both groups was low, selection bias is still a possibility.

In conclusion, fludrocortisone treatment, plasma potassium levels <4 mEq/L, and OSA were independently associated with increased risk, whereas the use of noninvasive ventilation was associated with decreased risk of SUDS in patients with FD. Most importantly, both OSA and low serum potassium levels are treatable risk factors. Initiation of noninvasive ventilation when required and discontinuation of fludrocortisone treatment should reduce the high incidence rate of SUDS in patients with FD.

REFERENCES

1. Riley CM, Day RL. Central autonomic dysfunction with defective lacrimation; report of five cases. Pediatrics. 1949; 3(4): 468–478.
2. Norcliffe-Kaufmann L, Slaugenhaupt SA, Kaufmann H. Familial dysautonomia: History, genotype, phenotype and translational research. Prog Neurobiol. 2017; 152: 131–148.
3. Blumenfeld A, Slaugenhaupt SA, Axelrod FB, et al. Localization of the gene for familial dysautonomia on chromosome 9 and definition of DNA markers for genetic diagnosis. Nat Genet. 1993; 4(2): 160–164.

4. Slaugenhaupt SA, Blumenfeld A, Gill SP, et al. Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet. 2001; 68(3): 598–605.
5. Mezey E, Parmalee A, Szalayova I, et al. Of splice and men: what does the distribution of IKAP mRNA in the rat tell us about the pathogenesis of familial dysautonomia? Brain Res. 2003; 983(1–2): 209–214.
6. Hunnicutt BJ, Chaverra M, George L, Lefcort F. IKAP/Elp1 is required in vivo for neurogenesis and neuronal survival, but not for neural crest migration. PLoS One. 2012; 7(2): e32050.
7. Macefield VG, Norcliffe-Kaufmann L, Gutiérrez J, Axelrod FB, Kaufmann H. Can loss of muscle spindle afferents explain the ataxic gait in Riley-Day syndrome? Brain. 2011; 134(Pt 11): 3198–3208.
8. Maayan HC. Respiratory aspects of Riley-Day Syndrome: familial dysautonomia. Paediatr Respir Rev. 2006; 7(Suppl 1): S258–S259.
9. Norcliffe-Kaufmann L, Axelrod F, Kaufmann H. Afferent baroreflex failure in familial dysautonomia. Neurology. 2010; 75(21): 1904–1911.
10. Norcliffe-Kaufmann L, Palma JA, Kaufmann H. Mother-induced hypertension in familial dysautonomia. Clin Auton Res. 2016; 26(1): 79–81.
11. Palma JA, Norcliffe-Kaufmann L, Fuente-Mora C, Percival L, Mendoza-Santiesteban C, Kaufmann H. Current treatments in familial dysautonomia. Expert Opin Pharmacother. 2014; 15(18): 2653–2671.
12. McNicholas WT, Rutherford R, Grossman R, Moldofsky H, Zamel N, Phillipson EA. Abnormal respiratory pattern generation during sleep in patients with autonomic dysfunction. Am Rev Respir Dis. 1983; 128(3): 429–433.
13. Gadoth N, Sokol J, Lavie P. Sleep structure and nocturnal disordered breathing in familial dysautonomia. J Neurol Sci. 1983; 60(1): 117–125.
14. Weese-Mayer DE, Kenny AS, Bennett HL, Ramirez JM, Leurgans SE. Familial dysautonomia: frequent, prolonged and severe hypoxemia during wakefulness and sleep. Pediatr Pulmonol. 2008; 43(3): 251–260.
15. Filler J, Smith AA, Stone S, Dancis J. Respiratory control in familial dysautonomia. J Pediatr. 1965; 66: 509–516.
16. Edelman NH, Cherniack NS, Lahiri S, Richards E, Fishman AP. The effects of abnormal sympathetic nervous function upon the ventilatory response to hypoxia. J Clin Invest. 1970; 49(6): 1153–1165.
17. Guilleminault C, Mondini S, Greenfield M. Abnormal respiratory pattern generation during sleep in patients with autonomic dysfunction. Am Rev Respir Dis. 1984; 129(3): 512–513.
18. Bernardi L, Hilz M, Stemper B, Passino C, Welsch G, Axelrod FB. Respiratory and cerebrovascular responses to hypoxia and hypercapnia in familial dysautonomia. Am J Respir Crit Care Med. 2003; 167(2): 141–149.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007; 4(10): e296.
20. Annegers JF. United States perspective on definitions and classifications. Epilepsia. 1997; 38(11 Suppl): S9–12.
21. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med. 2006; 354(22): 2368–2374.
22. Norcliffe-Kaufmann L, Axelrod FB, Kaufmann H. Developmental abnormalities, blood pressure variability and renal disease in Riley Day syndrome. J Hum Hypertens. 2013; 27(1): 51–55.
23. Cohen P, Solomon NH. Familial dysautonomia; case report with autopsy. J Pediatr. 1955; 46(6): 663–670.
24. Pearson J, Pytel BA, Grover-Johnson N, Axelrod F, Dancis J. Quantitative studies of dorsal root ganglia and neuropathologic observations on spinal cords in familial dysautonomia. J Neurol Sci. 1978; 35(1): 77–92.
25. Chobanian AV, Volicer L, Tifft CP, Gavras H, Liang CS, Faxon D. Mineralocorticoid-induced hypertension in patients with orthostatic hypotension. N Engl J Med. 1979; 301(2): 68–73.
26. Kjeldsen K. Hypokalemia and sudden cardiac death. Exp Clin Cardiol. 2010; 15(4): e96–e99.
27. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med. 2005; 352(12): 1206–1214.
28. Gami AS, Olson EJ, Shen WK, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. J Am Coll Cardiol. 2013; 62(7): 610–616.
29. Palma JA, Urrestarazu E, Lopez-Azcarate J, et al. Increased sympathetic and decreased parasympathetic cardiac tone in patients with sleep related alveolar hypoventilation. Sleep. 2013; 36(6): 933–940.
30. Kufoy E, Palma JA, Lopez J, et al. Changes in the heart rate variability in patients with obstructive sleep apnea and its response to acute CPAP treatment. PLoS One. 2012; 7(3): e33769.
31. Palma JA, Iriarte J, Fernandez S, et al. Long-term continuous positive airway pressure therapy improves cardiac autonomic tone during sleep in patients with obstructive sleep apnea. Clin Auton Res. 2015; 25(4): 225–232.
32. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol. 2008; 7(11): 1021–1031.
33. Shimohata T, Ozawa T, Nakayama H, Tomita M, Shinoda H, Nishizawa M. Frequency of nocturnal sudden death in patients with multiple system atrophy. J Neurol. 2008; 255(10): 1483–1485.
34. Rand CM, Patwari PP, Carroll MS, Weese-Mayer DE. Congenital central hypoventilation syndrome and sudden infant death syndrome: disorders of autonomic regulation. Semin Pediatr Neurol. 2013; 20(1): 44–55.
35. Shamsuzzaman AS, Somers VK, Knilans TK, Ackerman MJ, Wang Y, Amin RS. Obstructive sleep apnea in patients with congenital long QT syndrome: implications for increased risk of sudden cardiac death. Sleep. 2015; 38(7): 1113–1119.
36. Gold-von Simson G, Rutkowski M, Berlin D, Axelrod FB. Pacemakers in patients with familial dysautonomia–a review of experience with 20 patients. Clin Auton Res. 2005; 15(1): 15–20.
37. Solaimanzadeh I, Schlegel TT, Feiveson AH, et al. Advanced electrocardiographic predictors of mortality in familial dysautonomia. Auton Neurosci. 2008; 144(1–2): 76–82.
38. Saukko P, Knight B. The pathophysiology of death. In: Saukko P, Knight B, eds. Forensic pathology. 3rd ed. London: Hodder Arnold, 2004.

SUPPLEMENTARY MATERIAL

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DISCLOSURE STATEMENT

None declared.