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RESEARCH ARTICLE

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Fludrocortisone in patients with familial dysautonomia

Assessing effect on clinical parameters and gene expression

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Abstract The common familial dysautonomia (FD) mutation causes a splicing defect that leads to production of both wild-type (WT) and mutant (MU) *IKBKAP* mRNA. Because drugs may alter splicing, seven drugs, fludrocortisone, midodrine, diazepam, albuterol, clonidine, caffeine, and dopamine were screened. Since only fludrocortisone negatively altered gene expression, we assessed fludrocortisone's efficacy in treating postural hypotension, and its effect on survival and secondary long-term FD problems. For 341 FD patients we obtained demographic data and clinical information from the last Center evaluation (most current or prior to death) including mean blood pressures (supine, 1 min erect and 5 min erect) and history regarding syncope and presyncope symptoms. For 175 fludrocortisone-treated patients, data from the evaluation prior to start of fludrocortisone and from the last Center evaluation were compared. The fludrocortisone-treated patient cohort was compared to the non-treated patient cohort with respect to overall survival and event-free survival for crisis frequency, worsening gait, frequent fractures, spine curvature, renal insufficiency, and pacemaker insertion. Overall survivals of patients on fludrocortisone alone, on fludrocortisone and midodrine, and on neither drug were compared. Cumulative survival was significantly higher in fludrocortisone-treated patients than in non-treated patients during the first decade. In subsequent decades, the addition of midodrine improved cumulative survival. Fludrocortisone significantly increased mean blood pressures and decreased dizziness and leg cramping, but not headaches or syncope. Fludrocortisone was associated with more long-term problems, which may reflect more symptomatic status associated with longer survival. Our data suggest that fludrocortisone has clinical efficacy despite negative *in vitro* observations on gene expression.

Key words familial dysautonomia · fludrocortisone · mRNA splicing · midodrine · orthostatic hypotension

Introduction

Familial dysautonomia (FD) is an autosomal recessive disease affecting neuronal development [4, 17]. The FD gene, identified as *IKBKAP*, encodes the protein IKAP [1, 20]. The most common mutation, which is present on more than 99.5 % of all FD chromosomes, is a single T to C change at bp 6 of intron 20 in *IKBKAP*. This mutation causes a splicing alteration resulting in variable skipping

of exon 20 in the *IKBKAP* message producing both wild-type (WT) and mutant (MU) *IKBKAP* mRNA [1, 20]. The physiological consequence of the mutation is a reduction in cellular IKAP protein below a threshold. How this leads to neuronal death is not yet understood and so treatment of the protean clinical manifestations remains supportive [4, 7, 8]. Recent reports indicate that *IKBKAP* production and expression in cell culture can be altered by administration of various drugs [2, 3, 21]. However, none of the drugs presently considered as accepted FD treatments have been analyzed regarding ability to alter splicing and change WT:MU *IKBKAP* mRNA ratios initiating our screening of seven drugs. Two of the drugs screened are used to treat hypotension (fludrocortisone and midodrine) [5–8, 10], two are used to treat dysautonomic crisis and high blood pressure (diazepam and clonidine) [7, 8], and one, albuterol, is used commonly as an inhalation therapy in patients with respiratory problems. Caffeine was chosen because some FD patients report a need to consume coffee or tea to help raise their blood pressure. Dopamine was selected because it has been postulated that there may be increased release of this neurotransmitter during dysautonomic vomiting crises [4, 17].

Orthostatic hypotension is one of the most common problems experienced by individuals with FD [4–6]. Options for treatment of this particular problem are limited and there are really only two medications that have been specifically proposed for individuals with autonomic failure to ameliorate some of the lability and increase patient function – i. e., fludrocortisone (Florinef) and midodrine (Proamatine) [5, 6, 10]. Fludrocortisone's use in the FD population was first initiated in 1976, which gives us 29 years of experience, whereas trials of midodrine were not initiated until 1992, which gives us only 13 years of experience [10]. Presently, more than one-third of the surviving FD patient population is receiving fludrocortisone therapy on a daily basis to cope with postural hypotension [5–8]. Although midodrine's benefit in FD has been reported [10], fludrocortisone's effect on blood pressure in FD patients has not been analyzed. Thus, we assessed clinical and molecular effects of fludrocortisone in the FD population. We examined whether fludrocortisone use decreased symptoms associated with postural hypotension and improved blood pressure, and if fludrocortisone use prolonged life and decreased other long-term FD problems such as renal insufficiency, progressive ataxia, fractures, spinal curvature, and crisis frequency. We focused on whether fludrocortisone's clinical effect in the FD patient was consistent with its observed effect on gene expression.

Methods/design

Molecular analysis

FD lymphoblast lines were grown in RPMI-1640 supplemented with 2 mM L-glutamine and 1% penicillin/streptomycin and 10% fetal bovine serum (Invitrogen). Cells were cultured in the presence of 10 μM fludrocortisone, midodrine, diazepam, albuterol, clonidine, caffeine, and dopamine for 72 hours. RNA was extracted using Tri-Reagent™ (Molecular Research Center) and reverse transcription and *IKBKAP* PCR was performed as previously described [20, 21]. The ratio of WT:MU *IKBKAP* transcripts was determined following amplification as previously described [20, 21]. Quantitative real-time PCR (QPCR) was performed on three cell lines treated with fludrocortisone. Mutant *IKBKAP* mRNA was amplified using primers which span the exon 19–21 boundary: (5'-TGGTCTTCGTGACATCTTC, 3'-CAAAGCTTGTATTACAGACT). Total *IKBKAP* transcripts were amplified using primers in exons 6 and 8: (5'AATGCATCAGTCTGCTTTGCCCTG, 3'AGCAAACTCTCGGTTCCACACTCT). QPCR was performed using SYBR green mix (BioRad) on a BioRad Icycler with 50 fmol of each primer and 50 ng of total RNA. PCR conditions were as follows: 95 °C for 3 min; 40 cycles of 95 °C for 15 s, 60 °C for 1 min. All reactions were carried out in triplicate. The melting point was determined to rule out primer-dimer interference. Hypoxanthine ribosyltransferase (HPRT) was used as an internal control to correct for variations in RNA amount or efficiency of the RT reaction [12]. Three patient cell lines were tested, and serial dilutions made from one patient were used to generate the standard curve for calculation of relative gene expression.

Clinical Assessment

Patient population

From a worldwide database on 598 patients with familial dysautonomia (FD), we limited the review to 341 (57%) United States patients (163 males and 178 females) with information from annual examinations at the Dysautonomia Treatment and Evaluation Center at New York University Medical Center. Since May 1976, 175 (51.3%) patients received treatment with fludrocortisone. Indications for instituting fludrocortisone therapy were supine or erect mean blood pressures < 60 mmHg and/or the presence of presyncope or syncope.

All patients met clinical diagnostic criteria for FD [4]. All patients but one were homozygous for the common FD *IKBKAP* mutation.

Demographic data, including sex, birth date, survival status and information on long-term events were obtained on all patients, as well as clinical symptoms and blood pressures from the patient's last Center evaluation (most current or one prior to death). The study was conducted in accordance with the requirements of the NYU Institutional Research Board. Written consent for review of information had been obtained upon patient entry to the Center.

Assessing efficacy in treating orthostatic hypotension

For the fludrocortisone-treated patients, the date and age of start of use was noted, as well as length of use. Information from the patient's evaluation prior to start of fludrocortisone were recorded and compared to information obtained from the most current or last evaluation. Data included mean blood pressures (at 5 min supine, at 1 min erect and at 5 min erect) and the presence or absence of syncope and presyncope symptoms (dizziness, leg cramps, headaches). Dizziness included a positive history for dizzy spells, lightheadedness, blurring of vision or leg buckling. For the fludrocortisone-treated group we also noted any adverse effects and concurrent treatment with midodrine.

Assessing long-term effects

The patient's status in six clinical problem areas was noted.

Crises frequency. "Dysautonomic crises" are characterized by a constellation of symptoms that include nausea or retching as well as hypertension, tachycardia, diaphoresis, and erythematous skin blotching [4, 7, 8]. The frequency of crises, usually characteristic for a particular patient, was into four categories: daily to weekly, frequent (6/year or greater), infrequent and usually triggered by illness (1 to 5/year), and rare to no crises (less than 1/year).

Worsening gait. FD is progressive. With increasing age, frequently there is progressive sensory loss and development of an ataxic gait [5, 6, 10]. By adulthood a walker or a wheelchair may be required. Two cohorts, worsening gait or non-worsening gait, based on the need for walker or wheelchair were identified; age at the start of use was recorded.

Frequent fractures. The fracture rate in the FD population is as high as 40 % with a mean of 1.5 fractures per patient [16]. Patients were classified as low incidence fracture (0 or 1 fracture) or high incidence fracture (2 or more fractures). Date and age at second fracture was noted.

Severe spine curvature. Spinal deformities are common and affect 83 % of FD patients by age twenty years [14, 23]. Patients were classified as having severe spine curvature (a thoracic scoliosis curve > 40°, or kyphosis > 60° and/or previous spine surgery) or without severe spine curvature.

Renal insufficiency. Renal insufficiency and need for dialysis are potential complications for the adult FD patient [18]. Patients were divided into those with or without evidence of renal insufficiency based on a serum creatinine of 2 mg% or greater. Date when the serum creatinine was first recorded as 2 mg% or greater was noted.

Use of pacemaker. Hypotension has been associated with bradyarrhythmias and asystolic events. It has been suggested that these events contribute to sudden death in FD patients which has led to insertion of pacemakers [13]. We sorted patients into two groups, those with pacemaker and those without. For those patients with pacemakers, the dates of insertion were noted.

Statistical methods

Descriptive data on gender and decade of birth were presented as percentages; the distributions of these variables were compared for patients on fludrocortisone at any time during their lifetime (fludrocortisone-treated patient cohort) with patients never on fludrocortisone (non-treated patient cohort) using contingency table analyses.

Assessment of the effect of fludrocortisone and midodrine on overall survival

Kaplan-Meier survival analyses were used to compare cumulative survival for the fludrocortisone-treated patient cohort with the non-treated patient cohort. Survival time for each patient was estimated from date of birth. We recognize that patients were selected for treatment with fludrocortisone based on disease symptoms and clinical status and that patients who never received fludrocortisone probably differed in the clinical features of their illness. To enable a comparison of survival between these groups of patients, for each 10-year period, we assigned a patient to the fludrocortisone-treated group if they were on fludrocortisone for at least some time during the 10-year period. Kaplan-Meier analyses were also used to study the effects of midodrine on survival in the subset of fludrocortisone-treated patients on both drugs. For these analyses, the fludrocortisone-treated group was separated into patients who were simultaneously on fludrocortisone and midodrine for some time in the 10-year interval, and patients who were on fludrocortisone alone.

Assessing fludrocortisone's effect on orthostatic measures and symptoms

Paired t-tests were used to test for changes in blood pressure as a result of fludrocortisone therapy. Changes in the presence or absence of presyncopal symptoms before and after initiation of fludrocortisone were evaluated using the McNemar chi-square statistic.

Assessing fludrocortisone's effect on long-term problems

We examined the cumulative rates of occurrence of various complications to identify effects associated with fludrocortisone. For problems where date of onset was available, Kaplan-Meier survival analyses were used to compare the occurrence of these events in the fludrocortisone-treated and non-treated groups. For outcomes without dates of onset, either the Mann-Whitney U-test or chi-square analysis was used. Twenty-year intervals were used in analyses because there were few long-term events in the 10-year intervals.

Results

Fludrocortisone's effect on IKBKAP splicing

Of seven drugs, i. e., fludrocortisone, midodrine, diazepam, albuterol, clonidine, caffeine, and dopamine, only fludrocortisone was found to negatively alter the WT:MU *IKBKAP* ratio and resulted in a decrease of WT mRNA. The average WT:MU ratio in untreated lines was 1.6, while the average WT:MU ratio in cell lines treated with fludrocortisone was 0.91. QPCR designed to amplify only the mutant *IKBKAP* transcript was performed on three FD cell lines, and the relative increase in mutant *IKBKAP* following fludrocortisone when compared to the untreated lines was 1.6. However, no difference was observed in total *IKBKAP* expression following treatment.

Demographic characteristics of fludocortisone-treated patients

Table 1 compares the characteristics of fludrocortisone-treated patients with non-treated patients. The proportion of males in the fludrocortisone-treated group was 5 % higher than the proportion of males in the non-treated group. There was no statistical difference in sex distribution. The age distributions show that the majority (69.7 %) of fludrocortisone-treated patients were born after 1970. The mean age of start of fludrocortisone treatment was 14.7 years (range 1.9–51.6 years, s. d. = ± 9.6 years). For 41 % of fludrocortisone-treated patients, treatment was started by 10 years of age. Most often, once a patient was started on fludrocortisone, treatment was not stopped.

There were 16 patients (9 %) who reported adverse side effects from 2 weeks to 3 years after starting fludro-

Table 1 Gender and age distribution characteristics of treated and non-treated fludrocortisone groups

Characteristic	Fludrocortisone-treated group N = 175 Percent of total	Non-treated group N = 166 Percent of total	Chi-square	p value
Gender (% male)	50.3	45.2	0.89	0.35
Birth decade			34.6	< 0.001
1942–1950	2.9	10.2		
1950–1960	12.6	18.1		
1960–1970	14.9	19.9		
1970–1980	20.6	10.8		
1980–1990	23.4	12.0		
1990–2000	25.7	21.7		
2000–2004	0	7.2		

cortisone; some patients reported more than one symptom. Symptoms included hypertension (5 patients), dizziness (5 patients with one individual experiencing syncope), weakness (3 patients), headache (2 patients), edema (2 patients), and nausea (1 patient). Six of the 16 (37.5 %) could resume fludrocortisone after dosage was lowered. Of the 175 fludrocortisone-treated patients, 62 patients (35.4 %) were also taking midodrine. Three patients were on midodrine without fludrocortisone. The mean age of start of midodrine treatment was 21.3 years, (range 8.3–46.5 years, s. d. = ± 8.5 years). One-third of patients on both drugs started midodrine within five years of starting fludrocortisone and 66 % were on both drugs within 10 years.

Effect of fludrocortisone and midodrine on overall survival

Cumulative survival was significantly higher in the fludrocortisone-treated group than the non-treated group (logrank $\chi^2 = 21.5$, $p < 0.001$, median survival time for patients in the fludrocortisone-treated group: 35.8 years; for patients in the non-treated group: 23.4 years) (Fig. 1). These curves suggest that survival among groups differed more in the early years of life than in later years. To address this, additional analyses were performed to study survival by decade of age. During the first decade, cumulative survival was significantly higher in fludrocortisone-treated patients (97.3 % for treated patients vs. 89.7 % for non-treated patients, logrank $\chi^2 = 3.94$, $p = 0.047$). During this decade, only two of 73 fludrocortisone-treated patients died, as compared with 27 deaths in the 166 non-treated patient group (Fig. 1).

Over the entire study period, there was a significant difference in overall survival among the group on fludrocortisone alone, the group on fludrocortisone and midodrine, and the group on neither drug (logrank $\chi^2 = 30.69$, $p < 0.001$ (median survival time for patients on fludrocortisone alone: 32.8 years; for patients on both drugs, 37.9 years; for patients on neither drug: 22.2

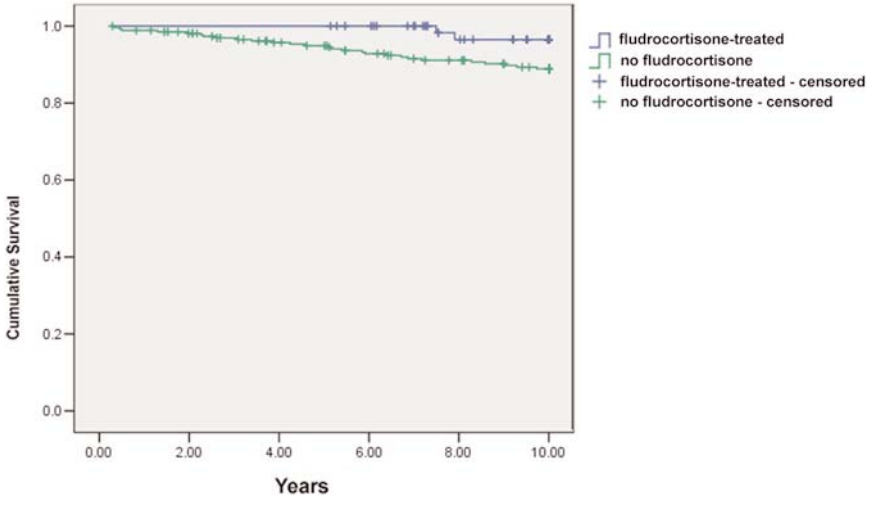

Fig. 1 Kaplan Meier survival curves comparing fludrocortisone treated and non-treated in the first 10 years of treatment

years). Fig. 2 presents the curves for the three groups; note cumulative survival is poorest when neither drug is used.

Fig. 3 provides survival curves for groups classified according to drugs that were taken during a given decade of life. These curves are conditional on a subject being alive at the beginning of a decade. The curves suggest that for each decade of life, patients with both drugs fared considerably better than patients in the other groups.

Fludrocortisone's efficacy in modifying blood pressures and symptoms

Overall supine and erect mean blood pressures were significantly increased by the last recorded evaluation. Table 2 provides a summary of blood pressure values and Table 3 lists the occurrence of specific orthostatic symptoms by presence or absence of each symptom before and after fludrocortisone therapy. Dizziness, the most frequent presyncopal symptom, and leg cramping, improved significantly with treatment.

Fludrocortisone's effect on long-term clinical problems

Results are listed in Table 4 and demonstrate that fludrocortisone treatment was associated with significant increases in likelihood of two or more fractures, severe spine curvature and pacemaker insertion. There was no negative or positive change in renal insufficiency, gait worsening or crisis frequency.

Discussion

Although the gene for FD has been identified as *IKBKAP*, the physiological consequence of the splicing mutation that results in a drastic reduction of cellular IKAP protein in certain tissues is not yet understood [1, 20]. The effect of the most common (splicing) mutation varies from tissue to tissue – neuronal tissues seem primarily to express MU mRNA; somatic tissues express roughly equal levels of WT and MU mRNA; and FD lymphoblast cell lines primarily express the normal product. Because the splicing mutation is tissue specific [20], the WT:MU *IKBKAP* mRNA ratio will vary depending on both the patient from whom the cell line is derived as well as the tissue examined. The effects of abnormal splicing and decreased amounts of WT *IKBKAP* mRNA on the protean clinical manifestations and symptomatology of FD are yet to be determined. However, it is possible that extent or rate of progression of disease may be influenced amount of functional WT *IKBKAP* mRNA. Thus investigations are underway to approach treatment of FD patients with drugs that alter *IKBKAP* splicing patterns [3, 21]. To date, two agents have been reported to increase the ratio of WT:MU *IKBKAP* mRNA ratio, epigallocatechin gallate (EGCG) and kinetin, a plant cytokinin [3, 21]. Accordingly we thought it appropriate to assess presently used interventions to determine if they had any impact on splicing. Of the drugs studied, only fludrocortisone had a negative effect. The other drugs tested had no effect on *IKBKAP* splicing. Interpretation of this cell culture finding, however, requires caution as *in vivo* and *in vitro* observations may not correlate.

Patients with familial dysautonomia (FD) almost invariably manifest orthostatic hypotension and often

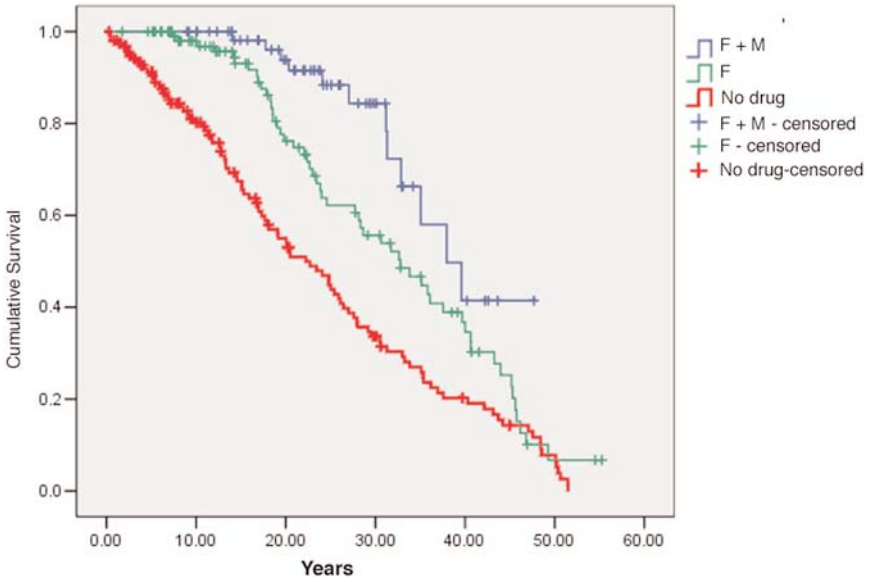

Fig. 2 Kaplan Meier survival curves comparing patients on fludrocortisone alone, patients on both fludrocortisone (F) and midodrine (M) and patients not treated with either of these two drugs (No drug) over the entire study period

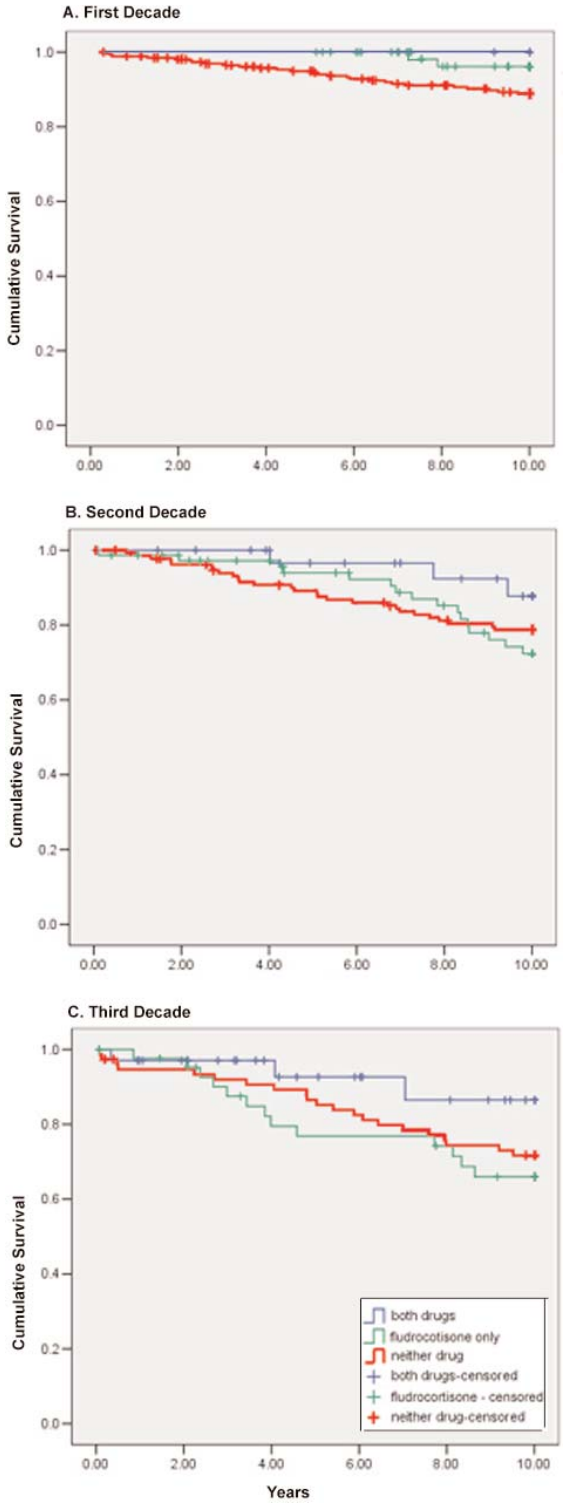

Fig. 3 Kaplan Meier survival curves comparing patients on fludrocortisone alone, patients on fludrocortisone and midodrine and patients on neither drug by individual decades. These curves are conditional on a subject being alive at the beginning of the interval. For years 10–20, the cumulative survival rates and the corresponding 95 % confidence intervals were 0.72, (0.61, 0.84) for the group on fludrocortisone alone and 0.88 (0.75, 1.0) for the group on both drugs; for years 20–30, these survival rates were 0.66 (0.55, 0.81) and 0.87 (0.72, 1.0) respectively

suffer severe functional limitations as a result [4–6]. There has also been speculation that some of the long-term sequelae such as dysautonomic crises, renal insufficiency and progressive ataxia may also be secondary to associated compromised perfusion of splanchnic, renal and cerebral vascular beds, respectively [9, 11, 15, 18, 22]. Options for treatment of orthostatic hypotension are limited and generally have been extrapolated from experience with other autonomic disorders. At present only two medications have been specifically proposed to ameliorate some of the lability and increase patient function – i. e., fludrocortisone (Florinef) and midodrine (Proamatine) [7, 8, 10]. In contrast to midodrine which was studied in clinical trials [10], fludrocortisone use was initiated earlier and never subjected to clinical trials in the FD population. Therefore, we reviewed our vast experience to determine if there was objective clinical efficacy, especially in light of the present information suggesting fludrocortisone has a negative genetic effect. Although this retrospective study was based on uncontrolled observations, we believe our data confirmed that fludrocortisone was an effective treatment for orthostatic hypotension in FD patients. The statistical analyses incorporated several approaches to deal with the potential bias that results from such uncontrolled studies. For example, the analyses by decade of life provide comparisons of fludrocortisone-treated patients to patients not treated with fludrocortisone. While we recognize that the decision to treat with fludrocortisone is based on clinical grounds, this is a large and unique patient experience.

Supine and erect mean blood pressures significantly increased after initiation of fludrocortisone therapy, and presyncopal symptoms of dizziness and leg cramping decreased. Although headaches are considered a common side effect of fludrocortisone therapy [19], we did not find a significant increase associated with its use. The increase in long-term sequelae associated with fludrocortisone use is of concern but may be a reflection of the longer survival of the fludrocortisone-treated population and the subsequent increase in the likelihood that these patients would experience these problems. The increased long-term sequelae may also reflect treatment bias in that more symptomatic patients were selected for treatment.

Because patients were selected for treatment with fludrocortisone based on clinical criteria, i. e., blood pressure measurements and clinical symptoms consistent with severe orthostatic intolerance, there was no truly comparable control group of non-treated patients since the latter were either less orthostatically impaired or non-compliant. However, we attempted to obtain comparability by examining survival in 10-year intervals starting from date of birth. In the early decades, many patients assigned to the fludrocortisone-treated group were not on fludrocortisone for the entire decade; only

Table 2 Mean blood pressures pre treatment and during treatment with fludrocortisone

Position	Mean BP pretreatment (mmHg)	Mean BP during treatment (mmHg)*	Increase (mmHg)	t value	df	p value
Supine (5 min)	98±26	117±30	19±34	7.02	159	< 0.001
Erect (1 min)	70±30	85±31	15±41	4.59	155	< 0.001
Erect (5 min)	64±31	77±28	13±40	3.53	109	0.001

* Based on measurements obtained at last evaluation

Table 3 Effect of fludrocortisone on clinical symptoms attributed to postural hypotension

Presence of symptom prior to fludrocortisone	n	Presence of symptom with fludrocortisone*		McNemar Chi square	p value
		Present	Absent		
Dizziness					
Present	122	50 (41 %)	72 (59 %)	47.5	< 0.001
Absent	33	9 (27.3 %)	24 (72.7 %)		
Leg cramps					
Present	56	18 (32.1 %)	38 (67.9 %)	11.3	0.001
Absent	95	13 (13.7 %)	82 (86.3 %)		
Syncope					
Present	55	21 (38.2 %)	34 (61.8 %)	3.1	0.076
Absent	104	20 (19.2 %)	84 (80.8 %)		
Headache					
Present	57	28 (49.1 %)	29 (50.9 %)	2.6	0.104
Absent	94	17 (18.1 %)	77 (81.9 %)		

Table 4 Prevalence of long-term sequelae of familial dysautonomia

Outcome	Prevalence in all 341 patients number(%)	Prevalence in 175 fludrocortisone patients number(%)	Test Statistic	p value
Crises			0.61*	0.54
Daily	70 (20.5 %)	31 (17.7 %)		
Frequent	53 (15.5 %)	31 (17.7 %)		
With illness	106 (31.1 %)	64 (36.6 %)		
Rare to none	112 (32.8 %)	49 (30.3 %)		
Worsening gait	67 (19.6 %)	42 (28 %)	0.26**	0.61
Spine curvature	153 (44.9 %)	95 (54.3 %)	12.9***	< 0.001
Fractures ≥ 2	98 (28.7 %)	66 (37.7 %)	27.6**	< 0.001
Renal insufficiency	33 (9.7 %)	21 (12 %)	0.85**	0.36
Pacemaker	23 (6.7 %)	19 (10.8 %)	9.67***	0.002

* Mann-Whitney U test – analyzed last reported assessment. Patients who were ever on fludrocortisone were compared to patients never on drug. ** logrank chi-square – analyzed events that occurred during the first 20 years of life. Patients on fludrocortisone by 20 years of age were compared to all others. *** Chi-square analysis – analyzed first event. Patients who were ever on fludrocortisone were compared to patients never on drug.

41 % of patients in the fludrocortisone-treated group were on the drug by 10 years of age. Since all but three patients remained on fludrocortisone once started, the cumulative proportion of patients on fludrocortisone for an entire decade increased over the decades. Because cumulative survival for the fludrocortisone-treated group will be affected by the time that a patient is not on fludrocortisone, the survival experience for patients assigned to the fludrocortisone group who are not on fludrocortisone for the entire period would likely bring the survival curves for the two groups closer together than if these patients were always on fludrocortisone. Thus any significant findings, positive or negative, would be enhanced or remain the same if patients were continuously treated. We found the positive effects of fludrocortisone occurred in very young patients and that after age

30, there were minimal differences in survival between the two groups. In later decades of life, increasing numbers of patients were on fludrocortisone over the entire decade, so that the effect of crossover to fludrocortisone was likely to be weak. By age 30, 91 % of patients had already been on fludrocortisone. It would be unreasonable to expect that in the later decades, significant results were masked by the patients not on fludrocortisone over the entire decade. Whether the marked improvement in cumulative survival with use of fludrocortisone in the early years is a true isolated effect of fludrocortisone alone or a beneficial impact of early intervention cannot be determined in this retrospective analysis. The improved mortality in the fludrocortisone treated group is particularly impressive if one speculates that treatment was initiated because patients were more symptomatic or more severe to begin with. The diminishing response to fludrocortisone in the later years may reflect the relentless progression of FD and thus fludrocortisone's inability to compensate for more extensive sympathetic denervation [4, 17]. Of interest, however, are the data indicating that additional use of midodrine in the later years further improves survival analysis. These data suggest that perhaps midodrine can be considered as an initial therapy rather than adjunctive treatment even in young children despite its not being approved as yet for use in the pediatric age range.

Our data suggest that fludrocortisone has clinical efficacy despite slightly negative *in vitro* observations on gene expression. Fludrocortisone use increased overall survival, improved mean blood pressures and decreased major presyncopal symptoms. It is possible that fludrocortisone's *in vivo* effect on splicing is different than its effect in cell culture or that its positive impact on overall health outweighs cell culture findings. Thus fludrocortisone's use for treatment of orthostatic hypotension should be determined on an individual basis.

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