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Increased risk of sudden death in untreated primary carnitine deficiency

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Abstract

Primary carnitine deficiency (PCD) affects fatty acid oxidation and is associated with cardiomyopathy and cardiac arrhythmia, but the risk of sudden death in PCD is unknown. The Faroe Islands have a high prevalence of PCD, 1:300. This study systematically investigated a possible association between untreated PCD and sudden death in young Faroese subjects. We investigated all medico-legal cases of sudden death between 1979 and 2012 among subjects below the age of 45. Stored biomaterial was examined with molecular genetic analysis to reveal PCD. We compared the prevalence of PCD among sudden death cases with that of the background population (0.23%) to calculate the odds ratio (OR) for sudden death with PCD. Biomaterial was available and genetically analyzed from 53 of 65 sudden death cases (82%) in the Faroe Islands. Six (one male and five females) of the 53 cases were homozygous for the PCD related c.95A>G mutation—a prevalence of 11.3% (95% CI 5%-23%) and an OR of 54.3 (95% CI 21-138, $P < .0001$) for the association between sudden death and untreated PCD. Only 11 of the 53 sudden death cases were women—of whom five were homozygous for the c.95A>G mutation (45.5%) yielding an OR of 348.8 (95% CI 94-1287, $P < .0001$) for the association between sudden death and untreated PCD in females. This study showed a strong association between sudden death and untreated PCD, especially in females.

KEYWORDS

Faroe Islands, primary carnitine deficiency, sudden death

1 | INTRODUCTION

Primary carnitine deficiency (PCD; OMIM #212140) causes continuous renal loss of carnitine leading to low plasma and intracellular carnitine levels, cellular instability, and potential cardiac arrhythmia.[1-7] PCD is an autosomal recessive disorder with an estimated prevalence of 1:142 000 in the United States and 1:40 000 in Japan, while more frequent in smaller isolated communities.[8-10]

The Faroe Islands are a small remote group of islands in the North Atlantic with a genetically homogenous population of 50 000 people whose ancient ancestors stemmed from the west coast of Norway and the British Isles.[11,12] Sudden death in two young Faroese individuals with untreated PCD raised a public demand in 2009 for preventive measures.[4] This prompted a nationwide screening program, which revealed a very high prevalence of PCD in the Faroe Islands (1:300).[8,13] Patients diagnosed with PCD—

both young and old—were put on lifelong supplementation with oral L-carnitine immediately as this was thought to prevent adverse symptoms.

Although sporadic case reports of sudden death in patients with PCD have been reported, no previous study has documented this presumed association.[4,14-17] Our aim was thus to systematically investigate if especially younger patients with PCD are at an increased risk of sudden death. By studying all cases of sudden death among subjects below the age of 45 years who were examined in the medico-legal system in the Faroe Islands between 1979 and 2012, and comparing the prevalence of genetically verified PCD among sudden death cases with the prevalence of PCD in the background population, we determined if there is an increased risk of sudden death among younger patients with untreated PCD.

2 | MATERIALS AND METHODS

2.1 | Medico-legal examination

If a person is found dead or died suddenly and unexpected, it is mandatory in the Faroe Islands to perform a medico-legal external examination of the deceased by the police and a medical examiner, who is a certified physician. The medical examiner has access to all information regarding the deceased including police and health records. The police will decide if a medico-legal autopsy should be performed based on a recommendation from the medical examiner and the circumstances at the death scene. Biomaterial is routinely taken and stored from all medico-legal autopsies. For the present study, records of all medico-legal examinations performed between 1979 and 2012 in the Faroe Islands were reviewed.

2.2 | Definition of sudden death

Sudden death was defined in a way to cover cases that might have died from severe cardiac arrhythmia/fibrillation secondary to an unexplained severe metabolic disturbance. Thus, the definition of sudden death in this study included the following situations:

1. Sudden unexpected death with presentation of symptoms within 24 hours of death or hospitalization.
2. Found dead with no obvious cause of death.

2.3 | Selection of cases for genetic evaluation

Cases below the age of 45 where a medico-legal autopsy had been performed were selected for further investigation, because biomaterial would likely have been stored from the autopsy. Autopsy reports were then carefully reviewed. If a case met our criteria for sudden death and biomaterial was available, the case was included for genetic analysis for PCD.

2.4 | Control group

Cases below the age of 45 years with a medico-legal autopsy and a well-documented specific other cause of death, for example, severe trauma, suicide, or obvious accidental death served as a control group. In 25 of these cases, biomaterial was genetically analyzed for PCD.

2.5 | PCD related sudden death abroad

Increased awareness and family tracing revealed supplementary cases of sudden death among young Faroese subjects living in either Faroe Islands, Denmark or Iceland at time of death, who were diagnosed with PCD postmortem with genetic analysis of stored biomaterial. These cases were included to describe the characteristics of sudden death cases, but they were not included in the statistical analysis when estimating the prevalence and risk of PCD.

2.6 | Biomaterial and genetic analysis

Biomaterial from medico-legal autopsies performed in the Faroe Islands has been stored either locally in the National Hospital or in the Institute of Forensic Medicine, at the University of Copenhagen, since 1979. Tissue samples were stored in blocks of paraffin.

DNA from available stored biomaterial was retrieved and molecular genetic analysis was performed in cases in which genetic status was not already established.[9] DNA was extracted by standard methods, and initially subjected to a targeted analysis for the presence of the common c.95A>G mutation in the *SLC22A5* gene (NM_003060.3). If cases were found to be heterozygous for c.95A>G, a subsequent analysis for other known mutations in the Faroe Islands was performed, ensuring analysis for genotypes found in 86% of all known living Faroese PCD patients.[18]

Primers and PCR conditions are available upon request.

2.7 | Nationwide PCD screening program

The screening program was established in 2009 to reveal as many undiagnosed children and adult PCD patients as possible in the Faroese population. It consisted of a voluntary biochemical-screening program, where all inhabitants were invited to have their blood carnitine levels assessed in dried blood spots. If levels of free carnitine were below 5 μmol/L, molecular analysis was performed to confirm possible PCD.[9] Furthermore, all neonatal filter paper cards collected

for neonatal screening from Faroese newborns dating back to 1986 were analyzed retrospectively to identify subjects with low levels of carnitine at birth. The program ensured that a large proportion of the Faroese population was screened especially among the younger age groups.[9]

2.8 | Statistics

Data analysis was performed using IBM SPSS Statistics Version 19 (SPSS Inc, Chicago, Illinois) and MedCalc version 16.4.1 (MedCalc Software, Ostend, Belgium). Odds ratio (OR), the SE and 95% confidence interval were calculated according to Altman.[19] The two proportion *Z*-test was used to test the difference between independent ratios. Linear regression was used to test the relationship between a decreasing prevalence of c.95A>G homozygotes with increasing age groups. The level of significance was set at $P < .05$.

The Faroese Ethics Committee approved this project.

3 | RESULTS

3.1 | Identification of sudden deaths in the Faroe Islands

The number of external examinations performed by the medical examiner between 1979 and 2012 was 1029 in total and the number of forensic autopsies was 335 (33%) (Figure 1). Three hundred and sixty-four examinations were performed on subjects below the age of 45 at the time of death and a medico-legal autopsy was performed in 138 of these cases (38%). Among the 138 cases, 65 met our criteria of sudden death.

3.2 | Genetic analysis

Biomaterial was available and genetically analyzed from 53 of the 65 sudden death cases (82%). We found six of the 53 cases to be homozygous for the c.95A>G mutation, which corresponds to a prevalence of 11.3% (95%CI 5%-23%). Five of the six c.95A>G homozygous cases were female, while only 11 of the 53 analyzed sudden death cases were women. Thus, the prevalence of c.95A>G homozygotes among female sudden death cases was 45.5% (95%CI 21.3-72) and 2.4% (95% CI 0.42-12.3) among male sudden death cases corresponding to at female to male ratio of 19.

No other PCD-related genotype was found among the remaining 47 sudden death cases.

Biomaterial was retrieved and genetically tested from 25 of the cases with a well-documented non-PCD related death—none was found to have a PCD-related genotype.

3.3 | Nationwide screening program (Background population)

The nationwide screening program for PCD examined 26 969 subjects aged 0 to 45 years yielding a participation

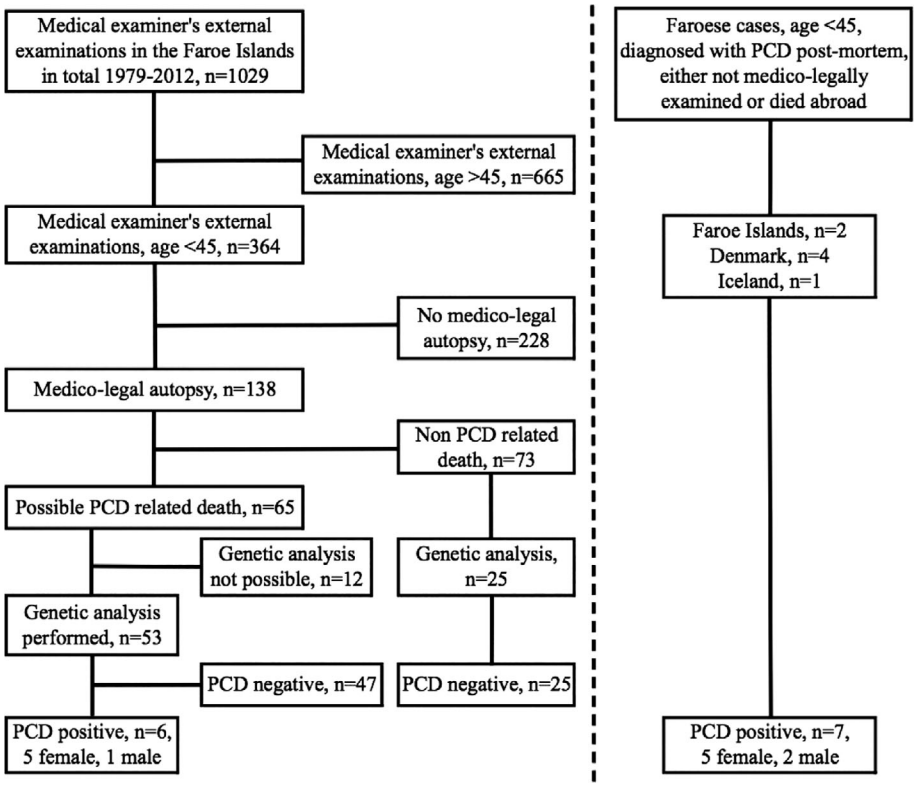

FIGURE 1 Flow chart

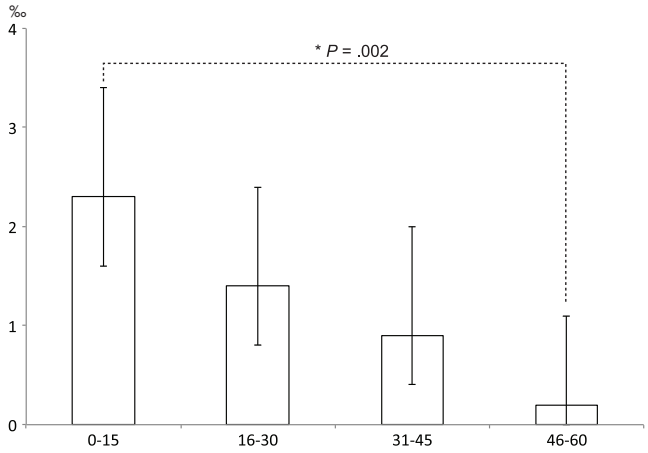

FIGURE 2 Prevalence of c.95A>G homozygotes in increasing age groups from 0 to 60 years (95%CI). There was a significant decline in c.95A>G homozygotes with increasing age ($P < .01$). And a significant difference between 0-15 and 46-60 age groups ($P = .002$)

TABLE 1 Number of c.95A>G homozygotes in increasing age groups and the number of individuals screened for PCD in the corresponding age groups distributed by gender

Age	0-15	16-30	31-45	46-60
c.95A>G homozygotes total	25	14	6	1
Female	12	4	3	1
Male	13	10	3	0
Screened total	10 657	9915	6397	4897
Male	5203	4905	2908	2150
Female	5454	5010	3489	2747

Abbreviation: PCD, primary carnitine deficiency.

rate of 91%—of whom 13 016 were males and 13 953 were females.

3.4 | Prevalence of c.95A>G homozygotes

Figure 2 shows a significant decline in the overall population prevalence of diagnosed c.95A>G homozygotes from 0-15, 16-30, 31-45, and 46-60 years ($P < .01$). The prevalence was significantly lower in the age group 46 to 60 compared to the 0 to 15 age group, $P = .002$ (Figure 2).

The number of c.95A>G homozygotes fell from 25 to 14, six and one in the respective age groups (Table 1).

3.5 | Association between sudden death and the c.95A>G homozygous genotype

Using the prevalence of c.95A>G homozygotes in the 0 to 15 age group as a benchmark for the true population prevalence, one would expect the prevalence of c.95A>G homozygotes among sudden death victims to be 0.23%. The prevalence of c.95A>G homozygotes among sudden death cases younger than 45 years was though 11.3%, yielding an OR of 54.3 (95% CI 21-138, $P < .0001$) for the association between sudden death and the c.95A>G homozygous genotype for male and females combined. The prevalence of c.95A>G homozygotes among the female sudden death cases (45.5%) compared with the female background prevalence of c.95A>G homozygotes in the 0 to 15 age group (0.24%) results in an OR of 348.8 (95% CI 94-1287, $P < .0001$). The corresponding OR for males only was 10.3 (95% CI 1-81, $P = .027$).

3.6 | Characteristics of c.95A>G homozygous sudden death cases

A further seven cases of sudden deaths (two in the Faroe Islands not medico-legally examined, four in Denmark and one in Iceland) among Faroese subjects below the age of 45, were recognized to have suffered untreated PCD at time of death. All were homozygous for the c.95A>G mutation—bringing the total number of registered PCD-related deaths among young Faroese individuals to 13; 10 female and 3 male (Table 2). In seven cases, the sudden death was associated with exposure to carnitine lowering antibiotics containing pivalic acid. No deaths occurred during physical activity, for example, during exercise or hard labor. Autopsy showed signs of cardiac hypertrophy in seven subjects ranging from moderate/severe in two patients and only slight in the other five. Cardiac arrhythmia (ventricular fibrillation, ventricular tachycardia, and asystoli) was the documented cause of death in seven individuals (Table 2). No case had a prior history of ischemic heart disease or diabetes.

TABLE 2 Overview of all 13 diagnosed Faroese sudden deaths cases associated with PCD

Gender	Male	Female	Total
	3 (23%)	10 (77%)	13
Mean age, years (range)	28 (21-37)	22 (1-43)	23 (1-43)
Place of death			
In hospital	0	7	7 (54%)
Home	2	3	5 (38%)
Other	1	0	1 (8%)
Documented cardiac arrhythmia	0	7	7 (54%)
Pivalic acid exposure	0	7	7 (54%)
Cardiac hypertrophy	3	4	7 (54%)

Abbreviation: PCD, primary carnitine deficiency.

4 | DISCUSSION

We here describe for the first time a strong association between sudden death and untreated PCD especially in females.

4.1 | c.95A>G mutation

In total, approximately 160 Faroese patients have now been diagnosed with PCD and receive L-carnitine supplementation.[13,18] All 13 sudden death cases diagnosed with PCD were homozygous for the c.95A>G mutation. Of the four different PCD-related mutations most frequently found in Faroese patients, the c.95A>G mutation is by far the most common in Faroese PCD patients with 86% being either homozygous or compound heterozygous for the c.95A>G mutation.[18] Patients homozygous for the c.95A>G mutation have the lowest residual OCTN2 transporter activity and mean free carnitine levels among the genotypes found in the Faroe Islands and seems to make them especially vulnerable to severe symptoms.[18]

As indicated in Figure 2, there are fewer than expected c.95A>G homozygotes above the age of 15 and especially between 46 and 60 years. There seem to be approximately 27 patients lacking in total in the age groups 16 to 60 years when compared to the prevalence in the 0 to 15 age group. It further indicates an association between premature death and untreated PCD among c.95A>G homozygous patients.

Untreated PCD patients around the world with genotypes with similarly poor residual OCTN2 transporter activity as c.95A>G homozygotes are likely at a similarly high risk of sudden death as untreated c.95A>G homozygotes.

4.2 | Cardiac arrhythmia

Cardiac arrhythmia was documented as cause of death in seven subjects. The seven subjects were admitted prior to suffering cardiac arrhythmia because of diffuse symptoms of affected consciousness and lethargy developed within 24 hours. The symptoms were likely caused by severe carnitine insufficiency-related hepatic dysfunction leading to hyperammonemia/encephalopathy. All seven subjects rapidly deteriorated and developed erratic cardiac arrhythmia with intractable ventricular fibrillation/tachycardia or bradycardia, asystole, and death. The other subjects suffered sudden death without documented prodromal symptoms and died outside hospital. Cardiac arrhythmia and metabolic dysfunction are due to abnormally low systemic and intracellular carnitine levels.[4,13,18,20,21] The excessive loss of carnitine in PCD patients is caused by dysfunctional plasma membrane OCTN2 carnitine transporters, which are not capable of adequately transporting carnitine intracellularly and prevent continued renal loss of carnitine in patients with PCD.[8,22] Carnitine is an amino acid derivative and has important roles of aiding the transport of long chain fatty acids across the inner mitochondrial membrane for beta-oxidation, stabilizing cellular membranes, and regulating fatty acid and carbohydrate metabolism.[23-25] Carnitine deficiency can thus lead to disturbances in cellular energy production and homeostasis and cause more or less severe symptoms in patients. Carnitine depletion can cause accumulation of fatty acids intracellularly, decreased detoxification, and removal of toxic acyl groups from mitochondria and an increase in myocardial reactive oxygen species, which could be arrhythmogenic and cause severe cardiac arrhythmia.[17,25-27] The pathophysiology is though not fully understood. A recent exercise study showed that c.95A>G homozygotes had a significantly impaired ability to utilize fatty acids for energy production compared to healthy controls.[28]

The cases of sudden death were not associated with exercise or hard physical activity—some occurred during the night while sleeping. This might in part be due to the increased reliance on energy production from fatty acids rather than carbohydrates in cells during rest—which could be detrimental in patients with PCD when suffering from critically low carnitine levels and thus impaired fatty acid oxidation and ultimately cardiac instability.

4.3 | Increased female to male ratio

Of the 13 known PCD related sudden deaths among Faroese subjects in the Faroe Islands and abroad, 10 were female. Furthermore, almost half of the female sudden death cases between 1979 and 2012 were homozygous for the c.95A>G—yielding a highly significant OR of 348.8 when compared with the background female population PCD prevalence. The corresponding male OR was 10.3. Preventive measures with screening and treatment for PCD could seemingly halve the incidence of sudden death among Faroese women. The apparent increased risk in female PCD subjects compared to male PCD subjects of suffering lethal complications is likely multifactorial. Females are more frequently prescribed antibiotics for especially urinary tract infections increasing the risk of exposure to carnitine lowering pivalic acid and thus increasing the risk of adverse symptoms in women with PCD.[4] Increased estrogen levels during fertile age also reduces blood carnitine in females.[9,29] Females with untreated PCD might thus experience critically low carnitine levels and a higher risk of symptoms and sudden death during young age.

4.4 | Pivalic acid

Seven patients (all female) were exposed shortly before their death to pivalic acid, which is used to aid the oral absorption

of certain antibiotics, but also causes a loss of carnitine in patients exposed to the substance.[4,30-32] Pivalic acid exposure might have led to a severe metabolic deterioration and ultimately lethal cardiac arrhythmia in some patients. Restrictions have been imposed on the use of pivalic acid containing antibiotics in the Faroe Islands.

Almost half of the discovered subjects had though not been exposed to pivalic acid before their death, which indicates that suffering from untreated PCD can be lethal in itself.

5 | LIMITATIONS

Our decision to only focus on medico-legally investigated deaths was based on the knowledge that the deaths were thoroughly investigated in the time frame chosen for this study and because of the availability of stored biomaterial. Medico-legally investigated deaths though only counted for approximately half of the total number of deaths in individuals younger than 45. Keeping in mind an apparent lack of 27 c.95A>G homozygotes in age groups older than 15, we seem to definitely have missed some PCD related deaths as we have only identified 13 in total. A steady emigration of especially young women might play a part—as we did not systematically investigate if emigrated young individuals had suffered sudden death abroad. Although our method of genetic analysis cannot rule out sudden deaths among Faroese PCD patients without the c.95A>G mutation, such genotypes are limited in the Faroe Islands. The residual OCTN2 transporter activity and carnitine levels are furthermore significantly higher in patients with genotypes without the c.95A>G mutation, hence the risk of undetected sudden death due to a genotype other than the c.95A>G mutation is likely negligible.[18]

6 | CONCLUSION

There is a strong relationship between untreated PCD among c.95A>G homozygotes and sudden death in especially females. There was a clear female overrepresentation among the c.95A>G homozygous sudden death cases. With adequate preventive measures and treatments, the rate of female sudden deaths in the Faroe Islands might be halved. Untreated PCD increases the risk of sudden death in young subjects especially females, and should be considered in cases of death of unknown cause.

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CONFLICT OF INTEREST

The corresponding author and all co-authors would like to declare no conflict of interest with regards to the content presented in this manuscript.

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