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Case Report

Autosomal dominant Carvajal plus syndrome due to the novel desmoplakin mutation c.1678A > T (p.Ile560Phe)

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ABSTRACT

Background: Carvajal syndrome is an autosomal dominant or autosomal recessive disorder, manifesting with dilated cardiomyopathy, woolly hair, and palmoplantar keratoma. Additional manifestations can be occasionally found. Carvajal syndrome may be due to mutations in the desmocollin-2, desmoplakin, or plakophilin-2 gene.
Methods and results: We report a family with Carvajal syndrome which additionally presented with hypoacusis, noncompaction, recurrent pharyngeal infections, oligodontia, and recurrent diarrhoea. Father and brother were also affected and had died suddenly, the father despite implantation of a cardioverter defibrillator (ICD). Genetic studies revealed the novel pathogenic mutation c.1678A > T in the desmoplakin gene resulting in the amino acid change Ile to Phe at position 560 in the index case and her brother. The index case underwent ICD implantation recently.
Conclusion: Phenotypic manifestations of Carvajal syndrome are even broader than so far anticipated, the number of mutations in the desmoplakin gene responsible for Carvajal syndrome is still increasing, and these patients require implantation of an ICD as soon as their diagnosis is established.

1. Introduction

Carvajal syndrome is a genetic disorder with autosomal dominant or autosomal recessive trait of inheritance [1]. Phenotypically, Carvajal syndrome manifests as dilated cardiomyopathy (dCMP), woolly hair, and palmoplantar keratoma [2]. Additional phenotypic manifestations include dental abnormalities, arrhythmogenic right ventricular dysplasia (ARVD), or leukonychia (Table 1) [3]. If particularly the right ventricle is involved the condition is termed Naxos syndrome, since the first patients with this constellation were reported from the Kykladian island of Naxos. Mutations in three genes have been detected to be causative for Carvajal syndrome [4]. These three genes include desmoglein-2, desmoplakin, and plakophilin-2. The pathogenetic role of other desmosomal and non-desmosomal proteins, such as desmocollin-2, plakoglobin, transmembrane protein-43 (TMEM43), the ryanodine receptor-2 (RYR2), desmin, LMNA, striatin, titin, and the transforming growth factor-β3 (TGF-β3), remains unclear [4]. Most likely the genetic heterogeneity is even broader than so far anticipated. In four cases was Carvajal syndrome associated with left ventricular hypertrabeculation, also known as noncompaction (LVHT) [2,3,5,6]. Here we report a family with autosomal dominant Carvajal syndrome due to a novel mutation in the desmoplakin gene. The detailed phenotypic features of the index patient of this family have been reported earlier [5].

2. Methods

For the genetic studies EDTA blood was taken and genomic DNA was extracted after ethical approval with informed consent had been obtained from the affected patient alive. The desmoplakin gene was PCR amplified using conditions described earlier. Purified PCR products were directly sequenced using an abi 3500 sequencer. The sequence was analysed using the Sequence Pilot software (JSI medical systems, Germany). All clinical investigations were conducted according to the Declaration of Helsinki Principles.

3. Results

In brief, the index patient is a 43 yo Caucasian female with left-sided hypoacusis since birth, oligodontia since age 10 y, recurrent pharyngeal infections between age 10 and 35 y, woolly hair since age 15 y, palmoplantar keratoma since age 15 y, recurrent diarrhoea since age 20 y, recurrent syncopes since age 22 y, and systolic dysfunction and LVHT since age 43 y. She currently did not fulfil the criteria for dCMP. Recently, she underwent implantation of an implantable cardioverter defibrillator (ICD). The family history was positive for Carvajal syndrome in her

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Table 1
Desmoplakin mutations so far reported in association with Carvajal/Naxos syndrome.

AOP (y)	Sex	EO	APF	Mutation	Reference
16	Female	Arab	ARVD, pemphigus-like skin	Gly2375Arg	[10]
29	Male	Caucasian	Leukonychia, oligodontia	c.1691C > T	[3]
10	Male	Caucasian	Brittle nails, oligodontia, ARVD	c.1691C > T	[3]
5	Male	Arab	External rotation of 5th toe	c.3924delG	[11]
59	Female	Arab	Onychogryphosis	c.7111C > A	[11]
21	Female	Arab	SCD	c.7111C > A	[11]
3	Male	nm	Alopecia, nail dystrophy	p.R1400X + p.R2284X	[12]
19	Female	Turkish	HTX, consanguineous parents	c.7780delT	[13]
14	Female	Caucasian	Bicuspid aortic valve	c.1748T > C (p.Leu583Pro)	[14]
22	Female	Caucasian	Dental agenesis, leukonychia	c.1691T > C (p.Thr564Ile)	[14]
10	Male	nm	LVHT	del5208-5209AG	[6]
11	Female	Indian	ARVD	c.3901C > T	[15]
17	Male	nm	Oligodontia	c.1790C > T	[16]
14	Male	Caucasian	Enamel defects, mucosal blistering	c.7964C > A, c.6310delA	[17]
14	Female	nm	Oligodontia, ARVD	c.7902delG	[7]
43	Female	Caucasian	Hypoacusis, oligodontia, LVHT	c.1678A > T	[present case]
6 patients	nm	Ecuadorian	Frameshift, truncated protein	c.7901delC	[18]
3	Female	nm	Oligodontia	c.6ß8 ins	[7]
3.5	Male	Turkish	Left and right dCMP (Naxos)	R1267X	[8]

AOP: age of patient, EO: ethnic origin, APF: phenotypic features in addition to Carvajal syndrome, ARVD: arrhythmogenic right ventricular dysplasia, nm: not mentioned, LE: leukoencephalopathy, SCD: sudden cardiac death, HTX: heart transplantation, LVHT: left ventricular hypertrabeculation.

father and her brother. Both have died from cardiac complications already. The father of the two had woolly hair, dCMP, and experienced recurrent ventricular tachycardias, from which he died despite implantation of an ICD. The brother had a history of recurrent syncopes, dental abnormalities, and dCMP. Despite the indication for implantation of an ICD, he refused this proposal because of bad experiences with the ICD of his father. Autopsy of the brother's heart showed marked right-ventricular dilatation and fatty degeneration of the right atrium.

Genetic testing at age 43 y in the index case by means of PCR and Sanger sequencing revealed the missense mutation c.1678A > T resulting in the amino acid change Ile to Phe at position 560 of the desmoplakin protein. According to the MutationT@ster and PolyPhen algorithms the mutation was assessed as pathogenic. The mutation has not been described in the 1000 Genomes Database or the Exome Aggregation Consortium Database. Structural modelling indicated that the mutation changed one amino acid located in the repeat spectrin 4 of the plakin domain of the protein leading probably to loss of the structural integrity of this domain. Luckily, it was possible to organise conserved post-mortem specimens from the autopsy of the deceased brother. Genetic analysis of this material confirmed that the brother also carried the same desmoplakin mutation c.1678A > T as the index patient. The father was phenotypically also affected but unfortunately no autopsy material from him for post-mortem genetic analysis was available anymore. According to the family tree a paternal autosomal dominant transmission is most likely.

4. Discussion

This study revealed a novel desmoplakin mutation in a family phenotypically manifesting as Carvajal syndrome. In addition to woolly hair, palmo-plantar keratoma, and systolic dysfunction, the index patient presented with unilateral hypoacusis since birth, oligodontia, recurrent pharyngeal infections during 25 y, and recurrent diarrhoea. In addition, LVHT was detected in the index case, which had been reported in altogether 4 cases with Carvajal syndrome including this patient so far [2,3,5,6]. Whether hypoacusis, pharyngeal infections, or recurrent diarrhoea can be attributed to the desmoplakin mutation remains speculative, since these abnormalities have not been reported in association with Carvajal syndrome. Most likely, these manifestations in the index case are unlinked to the mutation since they are non-specific and much more frequent due to other causes.

Desmoplakin is the most abundant protein of the desmosome [7]. Desmoplakin consists of a keratin-binding domain, a plakin domain, a N-terminal head domain, and a desmoplakin specific rod-domain [8]. The effect of the mutation on the function of the protein remains speculative since the detailed function of desmoplakin is still insufficiently understood. The mutation detected in the present case results in an amino acid change in the plakin domain of the protein. In this domain at least two further missense mutations have been described leading to Carvajal/Naxos syndrome with leukonychia and oligodontia [3] and to a right ventricular arrhythmogenic cardiomyopathy [9]. The mutation may result in a structural change of the spectrin 4 repeat leading to an insufficient recruitment of desmoplakin into desmosomes or may have a dominant-negative effect on the recruitment of other desmosomal proteins [7]. This scenario is conceivable since desmoplakin binds plakoglobin and plakophilins via its N-terminal domain. Desmoplakin mutations may not only cause Carvajal syndrome but also cutaneous and cardiac syndromes such as non-syndromic, isolated striate palmoplantar keratoderma, and non-syndromic ARVD [7]. Altogether 24 patients with Carvajal syndrome due to a desmoplakin mutation have been reported (Table 1). The phenotypic variability among our patients was higher than so far anticipated. Additional phenotypic features found in previously reported cases include oligodontia (n = 6), ARVD (n = 4), nail abnormalities (n = 4), LVHT (n = 2), alopecia (n = 1), bicuspid aortic valves (n = 1), and mucosal blistering (n = 1) (Table 1).

In conclusion, this study of a family with Carvajal syndrome shows that the phenotypic manifestations of this syndrome are possibly broader than so far anticipated, that the number of mutations in the desmoplakin gene responsible for Carvajal syndrome is still increasing, and that these patients require implantation of an ICD as soon as their diagnosis is established. Future studies must focus on the genotype-phenotype correlation more extensively since it remains unclear if certain mutations are more prone to be at risk of severe complications than others.

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