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Prevalence of neoplasms in definite and probable mitochondrial disorders

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ABSTRACT

There are some indications that the prevalence of benign and malign neoplasms is increased in patients with a mitochondrial disorder (MID). This study aimed at calculating the prevalence of malign and benign neoplasms in MID patients compared to the general population. Among 103 adult patients with definite or probable MID 16 had a malignancy (15.5%) and 11 (10.7%) a benign neoplasm. Four patients had thyroid cancer, three patients had prostate cancer, two patients each colon cancer, or ovarian cancer, and one each lung cancer, basalioma, Paget carcinoma of the skin, Bowen disease, renal cancer, and urinary bladder cancer. One patient had two carcinomas. Five patients had lipomas, two thyroid adenoma, and one each meningeoma, ovarian adenoma, hemangioma of the liver, and pituitary adenoma. Compared to the general population, the prevalence of malignancies was 3–4 fold increased in definite and probable MIDs. Compared to a cohort of myotonic dystrophy type-1 patients, the prevalence was 1.4 fold increased. In conclusion, adult MID patients seem to carry an increased risk to develop malignancy or a benign neoplasm. Females with a MID seem to be predominantly at risk to develop a neoplasm.

Introduction

Recently, it has been shown that the frequency of neoplasms is increased in patients with a mitochondrial disorder (MID) (Finsterer & Krexner, 2013; Schon et al., 2012). The most frequent among the malignancies in MID patients were breast cancer and the most frequent among the benign neoplasms were lipomas (Finsterer & Krexner, 2013). Females more frequently developed a neoplasm than males (Finsterer & Krexner, 2013). The present study aimed at assessing the prevalence of neoplasms in a larger cohort of MID patients diagnosed according to the Nijmegen criteria, an expansion of the Walker/Bernier criteria (Wolf & Smeitink, 2002), which type of tumours are the most prevalent in MID patients, and if there is a difference in the prevalence of neoplasms between MID patients and other neuromuscular disorders and the general population.

Patients and methods

Included were adult patients with a definite or probable MID, diagnosed according to the Nijmegen criteria (Wolf & Smeitink, 2002) over the last 23 y. Retrospectively evaluated were the charts of patients with syndromic or non-syndromic MIDs in whom the history was positive for a neoplasm. Malignancy was diagnosed upon the history and the histological report. The diagnosis of a malignancy was supported if the history was positive for tumour surgery, chemotherapy, or radiation. Semi-malign tumours were regarded as malignancies with a histological report describing malignant cells in the absence of hematological or lymphatic spreading (Leischner, 2014). Benign neoplasms were diagnosed in case of typical imaging findings, if histological investigations did not show malignant cells, if progression was absent or mild, and if focal or systemic spreading was absent during follow-up. Figures about the frequency of malignancies and benign neoplasms in the general population were taken from tumour registries of the Statistic Austria institute (Austria, n.d.) and from cancer statistics in the United States (Facts, 2015).

The diagnosis of a MID was based on the history, clinical exam, instrumental investigations, muscle biopsy, and genetic studies. For assessing the consistency of the diagnosis the clinical score of the Nijmegen criteria was applied allowing differentiation between definite and probable MIDs. The Nijmegen criteria were applied although being designed for diagnosing MIDs in children because the phenotypic similarities between pediatric and adult MIDs prevail and because the histological and genetic findings are similar in both age groups. Furthermore, the Nijmegen criteria gave similar results concerning the classification of certainty as the Bernier criteria in a study of 30 children (0–16 y) with MID. Possible MID patients were not included in the study since they are numerous and their diagnosis is poorly verified.

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Results

A definite MID was diagnosed in 41 patients, 24 males and 17 females, aged 27–82 y (Table 1). In 20 patients the diagnosis relied on a biochemical defect, in 23 patients on the genetic findings, and in 2 patients on both. Seven patients had a complex-I defect, three a complex-IV defect, and 10 multiple complex defects. The most common among the multiple complex defects was complex-I–IV defect. A point mutation within the mtDNA was found in 19 patients, a single mtDNA deletion in three patients, and mtDNA depletion in one patient. The Nijmegen score ranged between 8 and 11 points in these 41 patients. Among the 41 patients with definite MID 4 had a malignancy (9.8%) and 5 a benign neoplasm (12.2%) (Table 1). Two patients had thyroid cancer, and one each lung cancer and a basalioma. Among patients with a malignancy 2 were female and 2 were males. Age of the 4 patients with malignancy ranged between 50 and 83 y (mean: 65 y). Two patients had lipomas, and one patient each a meningeoma, thyroid adenoma, and ovarian adenoma.

A probable MID was diagnosed in 62 patients, 30 males and 32 females, aged 21 to 96 y. Among the 62 patients with probable MID, 12 had a malignancy (19.4%) and 6 a benign neoplasm (9.7%). The Nijmegen score ranged between 5 and 7. Three patients had a prostate cancer, two patients each colon cancer, thyroid cancer, or ovarian cancer, and one each a Paget tumour of the skin, Bowens disease, renal cancer, and urinary bladder cancer. A single patient had two carcinomas, one by one. Among patients with a malignancy, 7 were female and 5 were men. Age of the patients with malignancy ranged from 50 to 90 y (mean: 75 y). Among the benign neoplasms three patients had lipomas, and one each a hemangioma of the liver, pituitary adenoma, and thyroid adenoma.

Combining both groups, 16 of 103 patients with probable or definite MID (15.5%) had a malignancy and 11 of 103 (10.7%) a benign neoplasm. The most frequent of the malignancies was thyroid cancer (n = 4), followed by prostate cancer (n = 3), colon cancer (n = 2), and ovarian cancer (n = 2). Among those with a malignancy, 9 were female and 7 male. The most frequent of the benign neoplasms was the lipoma (n = 5) followed by thyroid adenoma (n = 2). Lifestyle, environmental stress factors, and medication were not made responsible for the development of malignancy in the 16 patients with malign neoplasms.

The prevalence of malignancies in the general population of Austria was 306,397 (excluding the 41 MID patients) at the end of 2014 (Austria, n.d.). Since the Austrian population was 8,406,000 in 2014 the prevalence of malignancies was 3.6%. In the United States 14.5 million patients with a malignancy were alive in January 2014 (Facts, 2015). Since the population of the United States was 318,900,000 in 2014 the prevalence of malignancies was 4.5%. Since 15.5% of the definite and probable MIDs of the present study had a malignancy, the prevalence of malignancies in MIDs was more than 4 times higher than that of the general population of Austria, and more than 3 times higher than that in the United States. No statistical data about benign neoplasms were available. As a disease control group 1081 patients with myotonic dystrophy type 1 (MD1) from a study of Gadalla et al., 2013 were included. Median age in these patients was 46 y, ranging from 0 to 86 y and 47.9% of the patients were male. Altogether, 11.4% developed cancer during follow-up in this cohort (Gadalla et al., 2013). The most frequent cancer types were ovarian cancer (n = 8), brain tumours (n = 6), and lung cancer (n = 4) (Gadalla et al., 2013). Thus, the rate of malignancy was 1.4 times higher among the MID patients as compared to the MD1 patients.

Discussion

In the present retrospective study malignancies occurred more frequently in MID patients as compared to MD1 patients, and to the general population of Austria, and the US. The prevalence of malignancies in MID patients was 3–4 fold higher compared to the general population, and 1.4 times higher compared to MD1 patients. In definite and probable MIDs 15% of the patients developed malignancy and 11% a benign neoplasm. Malignancies most frequently found in definite and probable MID patients were thyroid cancer and prostate cancer. Benign neoplasms most frequently found in MID patients were lipomas and thyroid adenomas. There was a slight female preponderance. MID patients with malignancy were older than MID patients without malignancy.

There are several levels of evidence that MIDs are associated with an increased risk to develop a neoplasm. First, several MID patients with a neoplasm have been reported (Finsterer & Krexner, 2013; Piccoli et al., 2012 Feb 21; Ohno et al., 2010; Sasano et al., 2009). Neoplasms not only occur in syndromic MIDs (Piccoli et al., 2012 Feb 21; Ohno et al., 2010) but also in non-syndromic MIDs (Table 2) (Sasano et al., 2009; Sangkhathat et al., 2005; Abu-Amero et al., 2004). Malignant neoplasms have been reported in patients with mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS) syndrome (Piccoli et al., 2012 Feb 21; Ohno et al., 2010; Sasano et al., 2009), myoclonic epilepsy with ragged-red fibers (MERRF) syndrome (Jones et al., 2012), Leber's hereditary optic neuropathy (LHON) (Zanssen & Buse, 2003; Lewis et al., 2010), Leigh syndrome (Cosson et al., 2008), and mitochondrial depletion syndrome (MDS) (Freisinger et al., 2006). Benign neoplasms have been reported in patients with MERRF syndrome (lipomas] (Teive et al., 2008; Schoffer & Grant, 2006; Träff et al., 1995; Larsson et al., 1995; Calabresi et al., 1994; Holme et al., 1993), LHON (pituitary adenoma (Mulliez et al., 2000), French-Canadian variant of Leigh syndrome (Arun et al., 2013), and CPEO (lipoma) (Suzuki et al., 2004). Second, there are reports showing that the amount of mtDNA mutations is increased in certain carcinoma cells, such as those of oncocytomas or breast cancer (Singh et al., 2009). In oncocytomas mtDNA mutations are made responsible for mitochondrial dysfunction and progression of tumour growth (Gasparre et al., 2013). Additionally, the MELAS mutation has been reported in colon cancer cells (Lorenc et al., 2003) and a number of mtDNA mutations were found in renal cell carcinoma cells (Meierhofer et al., 2006). Altogether, mtDNA mutations can be found in up to 80% of the various neoplasms (Grzybowska-Szatkowska & Slaska, 2012). Not only mtDNA mutations occur in malignancies but also mutations in *POLG1* (Singh et al., 2009). *POLG1* mutations can be found in two thirds of the breast cancers and are made responsible for decreased oxidative phosphorylation (OXPHOS) (Singh et al., 2009). Third, it has been recently reported that mutations in several nuclear genes encoding for mitochondrial components are associated with an increased cancer risk or may be even causative (van Gisbergen et al., 2015). These include the succinate dehydrogenase genes *SDHA*, *SDHB*,

Table 1
Prevalence of neoplasms in MIDs.

	Definite MIDs	Probable MIDs	Total
Number of patients (n)	41	62	103
Female/male ratio	17/24	32/30	49/54
Age (years)	27–82	21–96	21–96
Number of malignancies (n)	4	12	16
Female/male ratio	2/2	7/5	9/7
Number of benign neoplasms (n)	5	6	11
Female/male ratio	4/1	3/3	7/4