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Diabetes and Deafness

A New Genetic Syndrome

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1. Introduction

Although the classification of Diabetes Mellitus into Type 1 (with autoimmunity) **and Type 2** (without a utoimmunity) **is still relevant today, there is extensively more interest in the past years concerning spe cific subtypes of Diabetes**. The clinical evolution of these subtypes is particular and, in many cases, depend ent on the genetic heterogeneity.

The purpose of this article is to summarise the most important currently available data about the maternall y inherited deafness and diabetes (MIDD).

Sometimes starting from the study of 3-4 generations of the same family and going all the way to multice nter studies, the subject of this specific type of diabetes has raised significant interest in literature.

Because of the scientific progress registered in the last years in genetic research, now, more than ever, it is more accessible to understand the clinical expression of mitochondrial mutations. It is already a certainty that genetic factors are a part of diabetes' aetiology. Although the majority of genes involved have relative penetrance, there is also the particular case of some genes with dominant penetrance.

> **The Mature Onset Diabetes in Young (MODY) was the first of these subtypes that showed this kind of penetrance. Unlike MOD Y, the Maternally Inherited Diabetes and Deafness (MIDD) and i ts mitochondrial mutation have the specific of dominant inherita nce of the pathology by all children, with males having only the manifestation of the disease. With a prevalence of between 0.5% and 2,8% of the entire population of diabetes patients and charac teristically having this family aggregation, frequently misdiagnos ed as Type 1 or 2**

Diabetes, MIDD is rarely a highlighted manifestation [1].

MIDD was mostly studied on generations of affected families, up to the 4th generation in some cases . Only Gauillasseau *et al*., [2] and Laloi Michelin *et al*., [3] managed to include a more significant number of patients in multicenter studies in France. **The discovery of MIDD can be attributed to Dörner *et al.,*** [4] **and Köbberling and Tillil** [5] **who showed in their studies the involvement of the maternal in her it ance which was confirmed by a second study by Alcolado and Alcolado** [6]. It was initially unclear i f these maternal factors were referring to the intrauterine environment or genetic factors.

The acceptance that the maternal inheritance is mtADN related led the way to the research of mtDN A mutations. A certain pedigree was noticed by Lemkes *et al*., [7] in 1989 – all nine children of a mother diagnosed with MIDD expressed the same disease. Also, characteristic was the discovery in every diabetic patient of a variable degree of hearing loss. It was suggested that this maternal inheritance is specific to mtD NA mutations. Subsequently, a mtDNA analysis by Van den Ouwenland *et al*., [8]. Showed that an A to G transition in the 3243 position of the tRNAcodified mtDNA (Leu, UUR), one of the two transfer ARN gene s on the mitochondrial DNA, and the name of maternally inherited deafness and diabetes was proposed. The specific localisation of the mutation at the mitochondrial level seems to explain a large number of orga ns affected: the pancreas, the cochlea, the retina, the kidneys, muscles and brain.

2. Materials and methods

We reviewed the literature by searching the MEDLINE database for the most representative articles publish ed so far.

2.1 *Clinical aspects*

The close follow-up of the patients has led to the following consensus: in most cases, deafness precedes the clinical signs of impaired glucose tolerance. The manifestations appear in adulthood, at more than 20 years of age, with deafness occurring rapidly, diagnosed by audiometry, in most cases, it is bilateral, but incomplete and seems to affect more often and more severely the male patients. Practically it is the case of neurosensorial deafness that occurs associated with a perceived loss of high-frequency sounds, most comm only the patients having difficulties hearing sounds with a frequency higher than 5kHz [9].

The mechanism that causes impaired glucose tolerance in still to be understood. It seems that it could rese mble the mechanisms involved in MODY-2 (characterised by glucokinase mutations). J. Maasen [9] *et al*., suggest that we could be talking about a decrease of the ADP/ATP ratio in the cytosol all the way to a rese t of the pancreatic beta-cell glucose receptor. Although MODY-2 patients don’t have a progression to comp lications, in MIDD there is a tendency to age-related progressive deterioration, suggesting that there are mor e mechanisms involved than the one we already mentioned.

Unfortunately, we don’t have a clear image of the evolution of diabetes in MIDD, the vast majority of the st udied families having a rapid progression to insulinopenia while some requiring insulin therapy after approx imately ten years. There seems to be no implication of autoimmune processes in cases that phenotypically e volve as type 1 diabetes.

Concerning other conditions that may occur in MIDD, pigmentary retinopathy, a kind of retinal degeneration that does not impair visual acuity, but progressively narrows the visual field, is the most frequent. Moreover, another characteristic of MIDD patients is that none of the studied subjects was obese at the time of diagnosis. Most of them have a BMI under 20kg/m2, also suggesting the involvement of muscle damage.

2.2 ***Pathogenic aspects***

The mitochondria contain their DNA under the form of circular DNA with 16569 base pairs. **Each mitochondrion has some copies of mtDNA, and every cell has hundreds of mitochondria**. Therefore, a single cell carries up to thousands of mitochondrial genomes on the nuclear genome. Many of the mtDNA mutation's polymorphisms are related to ethnic background. Only a part of the mitochondrial components is codified in the mtDNA, such as ribosomal and transfer RNA and some of the proteins in the respiratory chain.

The majority of mitochondrial components are encoded in the nucleus. [10] The mtDNA in mammals is maternally inherited, because, during fertilisation, the mitochondria from the spermatozoon tail does not enter the oocyte. J. W. van den Ouweland *et al*., [11] succeeded in cloning cell lines that mostly contain mitochondrial DNA to study haplotype variations. Cells from two patients, both with 3243 mutations, but with distinct clinical phenotypes, have been used.

The first patient presented exemplary clinical aspects associated with MIDD (deafness and diabetes), while the other performed progressive non-diabetic kidney disease associated with deafness – an association known as an Alport-like syndrome. **It is well known that diseases associated with mitochondrial DNA impairment are characterised by variations of the percentage of mitochondria affected in various tissues and even between cells of the same tissue, a phenomenon called heteroplasmy** [3].

Levels of heteroplasmy from 0 to 100% have been found, but when this level reaches 80%, the cells develop lactic acidosis, have a particular mitochondria morphology and lose the ability to consume oxygen. Moreover, there is a lack of mitochondrial protein synthesis, suggesting that the mitochondria of patients with 3243 mutations are inactive. Based on these facts we could deduce that in tissues with high levels of heteroplasmy there is a lower oxidative elimination and a higher ADP/ATP ratio.

> **There is also a correlation with the clinical observation, a high level of heteroplasmy is associated with a clinical phenotype that includes a higher impairment of the beta-cell function, as it wa s quickly observed in amplitude studies on MIDD population. A decrease in muscle mitochondria function can lead to a reducti on in peripheral glucose uptake because glucose is partially conv erted into glycogen. Meanwhile, the other part is oxidised in the mitochondria. When oxidative elimination is low, it activates the process of glucose uptake stimulated by insulin.**

Another way in which mitochondrial dysfunction could affect glucose homeostasis is by modifying the pan creatic beta-cell function. Pancreatic beta-cell insulin secretion induced by glucose is dependent on the ADP /ATP ratio in the cell. It is possible that an impaired mitochondrial function affects this ratio, and, therefore , the glucose-related insulin release.

Since there are no biochemical studies of relevant tissues involved in glucose homeostasis in patients with 3243 mutations, one can only speculate on precise biochemical processes involved; emerging data sugge st that a decrease in insulin release is an essential factor in developing diabetes [9].

Extensive studies by Kadowaki group [12] and some others [9] have assessed insulin release capacity by or al glucose tolerance test, glucagon test and C peptide, and have proven that it was altered in most patients with MIDD. Defective secretion probably plays an essential role in this type of diabetes pathogenesis. I n 2009, M. Laloi Michelin *et al*., [3] publish an extensive study which included 89 patients diagnosed with MIDD (patients with MELAS syndrome-mitochondrial encephalopathy, lactic acidosis and stroke-like e pisodes having the same mutation, but with an unsteady presence of diabetes and other types of mitochondr ial diabetes have been excluded from the study).

The purpose of this study was to certify a correlation between phenotype severity and levels of periphera l leukocytes' heteroplasmy. Out of all 89 patients (40 men and 49 women), a number of eleven families with at least two members included in the study can be identified. Diabetes diagnosis was set by systematic al screening in 50.6% of cases, 33% at the occurrence of polyuria or ketoacidosis, and, respectively, 16.4% in pregnancy. Moreover, 63% have required insulin therapy in 6.1±7.2 years after diagnosis. The mean glyc osylated haemoglobin of the patients was 7.5±1.5%.

Regarding complications, diabetic retinopathy is present in 13% of patients, nephropathy (defined as microa lbuminuria, macroproteinuria >300 mg/dl RAC, and eGFR <60 ml/min) and hyperLDL-cholesterolemia in 44%, macroangiopathy in 22% of patients and associated with arterial hypertension in 37.6% of cases, diab etic cardiomyopathy (defined as the presence of left ventricular hypertrophy on ECG) in up to 41.6%, deafn ess in 90% of patients, and neuromuscular dysfunction in 34.6% of cases. Heteroplasmy levels are significa ntly higher in females than in males (21.6 vs 13.2%, P=0.018), without family aggregation.

There was a reverse correlation between heteroplasmy and BMI (R2=0.18; P<0.001). Furthermore, a direct relationship between heteroplasmy levels and glycosylated haemoglobin has been identified, both re maining significant after the age of blood collection and gender adjustments. The inversely proportional cor relation between heteroplasmy and age at diagnosis has lost significance after age and gender adjustments. No relationship between heteroplasmy levels and the requirement of insulin therapy or its delay has bee n identified.

The fact that the first 4 patients by levels of heteroplasmy (between 61 and 85%) presented more severe fo rms of illness, with inaugural ketoacidosis onset in 2 out of 4 cases, 3 of whom required insulin therapy, c onfirms once again that the degree of heteroplasmy in m3243 DNA mutation in circulating leukocytes c ould be, at least partially, responsible for the variability of clinical manifestations observed in this rare for m of diabetes.

3. Discussions and Conclusions

The targeted diagnosis of this particular type of diabetes becomes a priority not only because of its strong p enetrance but also because of its broad and relatively nonspecific spectre of clinical manifestations. **Eve n though the discovery of the genetic mutation remains the golden standard for diagnosis, a series of pathological and phenotypical criteria can guide us toward the correct diagnosis**.

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