Endocrinopatie multiple (deficit di ormone dell'accrescimento, ipotiroidismo autoimmune e diabete mellito) nella syndrome di Kearns-Sayre

Multiple endocrinopathies (growth hormone deficiency, autoimmune hypothyroidism and diabetes mellitus) in Kearns-Sayre syndrome

A. Berio,[1] A. Piazzi[1]

Key words: multiple endocrinopathies, Kearns-Sayre syndrome

Abstract

Kearns-Sayre syndrome is characterized by onset before 20 years, chronic progressive external opthalmoplegia, pigmentary retinal degeneration, and ataxia (and/or hearth block, and/or high protein content in the cerebrospinal fluid) in the presence of mtDNA rearrangements. Multiple endocrine dysfunction associated with this syndrome was rarely reported. In this paper, the Authors report on a female patient with Kearns-Sayre syndrome with large heteroplasmic mtDNA deletion, absence of cytochrome c oxidase in many muscle fibers, partial GH deficiency, hypothyroidism and subsequently insulin dependent diabetes mellitus (IDDM). Anti-thyroid peroxidase and antithyreoglobulin antibodies were present in high titer in serum while anti-islet cell antibodies were absent. The patient developed thyroiditis with Hashimoto encephalopathy.

The presence of GH deficiency, autoimmune thyroiditis with hypothyroidism and IDDM distinguishes this case from others and confirms the association of Kearns-Sayre syndrome with multiple endocrine dysfunction.

Hashimoto encephalopathy and anti-thyroideal antibodies suggest that in this patient, predisposed by a genetic factor (a mitochondrial deletion) anti-thyroideal antibodies may have contributed to the hypothyroidism and, by interfering with cerebral mitochondrial function, may have caused the encephalopathy. GH deficiency and IDDM can be attributed to oxidative phosphorylation deficiency but the autoimmunity may also have played a role in the production of glandular insufficiencies. It seems important to search for endocrine autoimmunity in every case of KSS.

Riassunto

Raramente sono state riportate disfunzioni endocrine multiple nella syndrome di Kearns-Sayre (SKS, caratterizzata da inizio prima di 20 anni, oftalmoplegia cronica, degenerazione pigmentaria della retina od atassia o blocco cardiaco od alto contenuto di proteine nel liquor).

Con questo lavoro, gli AA riportano un caso di SKS con estesa delezione eteroplasmica del mtDNA e deficit endocrino multiplo (difetto di GH, ipotiroidismo, diabete mellito insulino-dipendente (IDDM), in cui erano presenti anticorpi antiperossidasi ed antitireoglobulina, per cui fu diagnosticata tiroidine autoimmune, ma erano assenti anticorpi anti-isole pancreatiche. Successivamente la paziente presentò encefalopatia di Hashimoto.

L'associazione di deficit di GH di tiroidite autoimmune, ipotiroidismo ed IDDM è unica nella SKS e realizza una forma parziale di sindrome autoimmune polighiandolare tipo II. La presenza di anticorpi antitiroidei e l'encefalopatia di Hashimoto nella SKS suggeriscono che in questa paziente, predisposta da un fattore genetico (la delezione mitocondriale) gli anticorpi antitiroidei possono aver contribuito all'ipotiroidismo ed, interferendo con la funzione mitocondriale cerebrale, possono aver causato l'encefalopatia. Il deficit di GH e l'IDDM sono attribuibili al deficit della fosforilazione ossidativa, ma l'autoimmunità può essere stata sinergica nelle produzione dell'insufficienza ghiandolare.

[1] Department of Pediatric Sciences "G. De Toni" University of Genoa, Genoa, Italy.

Indirizzo per la corrispondenza (Corresponding author):
Prof. A. Berio
Dipartimento di ScienzePediatriche, Università di Genova
Largo G. Gaslini 5, 16100, Genoa, Italy.
Fax +39010-3538265
e-mail address: agostinoberio@ospedale-gaslini.ge.it
Tel. +39010-5636248

Gli AA concludono che in ogni caso di SKS è opportuno ricercare l'autoimmunità ed in particolare quella diretta contro le ghiandole endocrine.

Introduction

Endocrine disturbances seem to be frequent in mitochondrial diseases and particularly in Kearns-Sayre syndrome (KSS),[1,2,3] a disease characterized by progressive ophthalmoplegia, pigmentary retinopathy, ataxia (or cardiac conduction defect or raised proteins in cerebrospinal fluid), and onset before 20 years of age [1].We report here on a case of KSS presenting multiple endocrinopathies, namely growth hormone (GH) deficiency, hypothyroidism with Hashimoto encephalopathy, and diabetes mellitus.

A female proposita presented at 10 years of age with typical KSS (ophthalmoplegia, pigmentary retinopathy, ataxia), short stature (121 cm < 3rd P), low weight (20 Kg < 3rd P), GH partial deficiency (maximum GH level after clonidine and arginine below 10 ng/ml; IgF I=65 ng/ml (nv 133-667)) and autoimmune thyroiditis (antithyreoglobulin and antimicrosomal antibodies I:2505 and I:2200, respectively; NV in both < I:300) with normal thyroid hormones in serum. MRI of the brain showed a hyperintense area of the mesencephalon. Muscle biopsy showed numerous ragged red fibers and absence of cytochrome c oxidase in many fibers, accumulation and abnormalities of mitochondria on Gomori trichrome stain. Southern blot and PCR of muscle fibers showed a 5.5 Kb heteroplasmic deletion of mtDNA.

Glycemia, urea, cholesterolemia, ESR, full blood count, serum electrolytes, ECG and EEG were normal. Subsequently, EEG showed runs of bilateral fronto-temporal and left temporo-occipital sharp waves, diffuse slow theta waves (5-6 Hz, 35microV) in all the other regions, and bursts of frontal polyspikes bilaterally. Treatment was started with coenzyme Q (50-100 mg/day) and, for diabetes mellitus prevention, a diet high in foods with low glycemic index and low in sugars with high glycemic index.[4]

From the age of 13 years, the patient had showed chronic depression, with improvement and worsening phases until the age of 17 years, when she complained of visual hallucinations and tremor. Slight enlargement of the thyroid gland and patellar hyperreflexia were observed.

A diagnosis of autoimmune thyroiditis with the diffuse progressive type of Hashimoto encephalopathy[4,5] was made. After 6 months, the patient presented with repeated syncopal attacks and complete atrio-ventricular block (Morgagni-Adams-Stokes syndrome); after permanent ventricular pacemaker insertion, no further syncopal attacks were observed. At age 18 years, raised antithyreoglobulin and antithyreoperoxidase antibodies [(390 IU-660 IU/ml (nv 1-195) and 49-62 IU/ml (nv 0-32), respectively] and raised TSH (4.6-5.8 micro U/ml) with normal T3, T4 thyroid hormones were recorded. A diagnosis of compensated hypothyroidism was made. At 20 years of age, antithyreoperoxidase antibodies were persistently high (97 IU/ml), but TSH, T3 and T4 were normal. At age 21 years, antithyreoglobulin and antithyreoperoxidase antibodies were 174 IU/ml and 108 IU/ml, respectively. Serum ACTH was normal (22.4 pg/ml: nv 10-46). Subsequently, the patient was relatively well.

At 22 years 6 months of age, the girl presented with low weight, bilateral basal pneumonia and respiratory failure. She received ventilatory support. Glycemia was repeteadly normal, antiperoxidase antibodies were raised (105 IU/ml). Gastrostomy (PEG) was performed and parenteral foods were supplied.

At home, other physicians replaced the diet with another one specific for enteral nutrition, containing maltodextrines, fructooligosaccharides, oils, medium chain triglycerides, fibres, vitamins, carnitine. At age 25 years, the patient presented with diabetes mellitus (fasting glycemia: 298 mg/dl, raised glycated Hb, high triglycerides: 274 mg/dl). ICA were negative. Weight was 60 Kg; height 150 cm. Insulin therapy was introduced and at 27 years of age the patient presented with insulin dependent diabetes mellitus (IDDM).

Discussion

The presence of GH deficiency, compensated hypothyroidism, and IDDM led to the diagnosis of KSS with multiple endocrinopathies, a condition sometimes due to autoimmunity (autoimmune polyglandular syndrome (APS) type II, characterized by Addisons's disease, thyroid autoimmune disease and insulin dependent diabetes mellitus). It is debated whether patients without Addison's disease, but with IDDM, thyroid autoimmune disease, or autoimmune atrophic gastritis/pernicious anemia should be classified as having type II APS.[6]

In KSS, diabetes mellitus (DM) was found to be associated. Twentynine of 226 patients with KSS presented with DM (13 with insulin dependent diabetes mellitus).[2] In KSS, mtDNA mitochondrial deletions presenting a variety of sizes or duplications are usually associated with wild type mtDNA (heteroplasmy). When the proportion of mutant mtDNA exceeds a certain threshold for an organ, the ATP synthesis of the mitochondria may become inadequate and symptoms appear.[3] DM in KSS is attributable to a mtDNA mutation.[3] Two types of mtDNA mutations are closely associated with DM in this condition, both being major rearrangements, i.e. heteroplasmic deletions and tandem duplications.[7,8,9] In addition to partial duplication, more complex mtDNA rearrangements involving deletion mtDNA monomers and dimers (pleioplasmy) have been observed in some cases of KSS with DM.[8,10] The distribution of mtDNA rearrangements is widespread.[8,9,10]

The mutations of mtDNA cause an impaired oxidative phosphorylation with ATP synthesis defects, because mtDNA mutations may inhibit mitochondrial function and insulin synthesis/ function. Initially, DM in KSS is not insulin-dependent, but the patients become progressively insulin deficient and, finally, almost all need insulin for the metabolic control [3]. Another subtype of diabetes mellitus is also present in mitochondrial diseases, i.e. non insulin dependent diabetes mellitus (NIDDM) and maternally transmitted deafness , which is due to a point mutation in the tRNA leu (UUR) gene, the so called 3243A to G transition.[7,11] In a study by

Kobayashi et al.,[12] 13 of 31 patients with NIDDM and maternally transmitted deafness presented with circulating islet cell antibodies and pancreatic damage. To our knowledge in patients with DM and KSS, anti-islet cell antibodies (ICA), anti-glutamic acid decarboxylase (GAD) antibodies or anti-insulin antibodies (IA2) have not been reported in the literature. The case reported by Ohno et al.[13] presented with **incomplete** KSS phenotype, 22,532 bp deletion as well as A 3243 G mutation and the features of APS II polyendocrinopathy (Addison's disease, autoimmune thyroiditis, ovarian failure, and IDDM) with anti-islet cell antibodies.

Given the central role of mitochondria in pancreatic β-cells and in skeletal muscle metabolism, the mitochondrial defect in mitochondrial disease[5] may predispose the cells to destruction, with consequent diabetes, via defective insulin production.[14]

Isolated DM associated with KSS was repeatedly reported. After the study by Harvey and Barnett,[2] other cases of this association were reported.[15,16,17] To our knowledge, in these latter cases neither antipancreas nor anti-insulin antibodies were reported. DM in KSS was also found in association with another single endocrinopathy, mainly hypoparathyroidism.[2,18,19] However, in these studies no association with anti-GAD or ICA antibodies was reported. The association of IDDM or carbohydrate intolerance with GH deficiency was reported by Kuriyama et al.[20] and by Mohri et al.,[21] who did not mention whether anti-GAD or ICA antibodies were associated. The association of IDDM with hypoparathyroidism with undetectable ICA and anti-parathyroid antibodies was reported by Isotani.[19]

Wilichowski et al.[10] reported on a similar case, in which antipancreas tissue, antithyroideal and antiparathyroideal antibodies were not detectable.

Artuch et al.[3] reported on an obese child with KSS, DM and adrenal insufficiency not presenting ICA, GAD, anti-insulin antibodies (IRI), anti-thyreoperoxidase, or anti-thyreoglobulin antibodies.

The association of DM with some endocrinopathies and auto-antibodies is rarely reported in KSS. Toppet et al. [22] reported on a case of KSS with hypoparathyroidism, diabetes mellitus, ANA, anti-anterior pituitary antibodies and anti-smooth muscle antibodies. Harvey and Barnett[2] reported on the association among hypoparathyroidism, hypothyroidism and IDDM in a patient with KSS presenting weak microsomal antithyroideal, antinuclear and anti-smooth muscle antibodies.

Sanaker et al.[22] reported on a female patient with KSS, hypothyroidism, autoimmune thyroiditis, positive peroxidase antibodies, Addison's disease with 21-hydroxylase antibodies and transitory hyperglycemia requiring insulin therapy in which neither GAD nor 1A2 antibodies were detected.

The condition present in our patient is unique in the literature because of the association among GH deficiency, hypothyroidism, thyroiditis, and IDDM.

GH deficiency, repeteadly reported in KSS, is commonly attributed to OXPHOS deficiency with diminished energy production and GH secretion failure[24] or to hypothalamic lesion. IDDM observed in our patient without the presence of ICA seems quite different from maternally transmitted DM with deafness frequently associated with anti-islet cell antibodies and a lean body type[3,11] , and may be due to OXPHOS deficiency in pancreatic islet cells, with insulin secretion failure.[9] The presence of serum anti-thyroideal antibodies in our patient raises the question whether they are a benign epiphenomenon or are causally related to thyroid dysfunction. In KSS, hypothyroidism associated with mitochondrial disease could be due to OXPHOS deficiency in the thyroid gland, with consequent failure in the production of thyroid hormones.[2] In our case, in which antithyroideal antibodies were constantly present for years , the mechanism may be more complex. The presence of antithyreoglobulin and antiperoxidase antibodies suggests that in our patient, predisposed by a genetic factor (i.e. a mitochondrial deletion), antithyroideal antibodies may have contributed to the endocrinopathy. We hypothesize that OXPHOS deficiency could cause a thyroid cell injury, followed by autoantigen production and presentation of auto-antigens to the immune system with autoantibody production[13] which, by interfering with mitochondrial cerebral function, may have caused Hashimoto encephalopathy.

In conclusion, it seems important to study the endocrine system and search for antibodies against the endocrine system in every case of KSS.

We thank Anna Capurro for her help in revising the manuscript.

References

1 Rowland LP, Hays AP, Di Mauro S. Diverse clinical disorders associated with morphological abnormalities in mitochondria. In Scarlato G, Cerri C editors Mitochondrial pathology in muscle disease. Piccin Ed., Padova, 1983.

2 Harvey JN, Barnett D. Endocrine dysfunction in Kearns-Sayre syndrome. Clin Endocrinol, 1992; 37: 97-104.

3 Artuch R, Pavia C, Playan A, Vilaseca MA, Colomer J, Valls C et al. Multiple endocrine involvement in two pediatric patients with Kearns-Sayre syndrome. Horm Res 1998; 50: 99-104.

4 Foster-Powell K, Holt SHA, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002; 76: 5-56.

5 Kothbauer-Margreiter K, Sturzenegger M, Komor K, Baumgartner K, Hess CW. Encephalopathy associated with Hashimoto thyroiditis: diagnosis and treatment.J N eurol 1996; 243: 585-593.

6 Riley WJ. Autoimmune polyglandular syndromes. Horm Res 1992; 38 (suppl 2): 9-15.

7 Ballinger SW, Shoffner JM, Gebhart S, Koontz DA, Wallace D. Mitochondrial diabetes revisited. Nat Genetics 1994; 7: 458-459.

8 Poulton J, Morten KJ, Weber K, Brown GK, Bindoff L. Are duplications of mitochondrial DNA characteristic of Kearns-Sayre syndrome? Hum Mol Gen 1994; 3: 947-951.

9 Poulton J, O'Rahilly S, Morten KJ, Clark A. Mitochondrial DNA, diabetes and pancreatic pathology in Kearns-Sayre syndrome. Diabetologia 1995; 38: 868-871.

10 Wilichowski E, Gruters A, Kruse K, Rating D, Beetz R, Korenke GE et al. Hypoparathyroidism and deafness associated with pleioplasmic large scale rearrangements of mitochondrial DNA. Pediatric Research 1997; 41: 193-200.

[11] Van den Ouveland JMV, Lemkes HHPJ, Ruitembeck W, Sandkuijl LA, De Vijlder MF, Struvemberg PAA et al.. Mutation in mitochondrial tRNA LEU (UUR) gene in a large tRNA pedigree with maternally transmitted type II diabetes mellitus and deafness. Nat Genet 1992; 1: 368-371.

[12] Kobayashi T, Oka J, Katagiri H et al. Association between HLA and islet cells antibodies in diabetic patients with a mtDNA mutation at base pair 3243. Diabetology 1996; 39: 1196-2000.

[13] Ohno K, Yamamoto M, Engel A, Harper M, Roberts LR, Tan GH et al. Melas and Kearns-Sayre type co-mutation with myopathy and polyendocrinopathy. Ann Neurology 1996; 39: 761-766.

[14] Lowell BB, Shulman G. Mitochondrial dysfunction and Type 2 diabetes. Science 2005; 307: 384-387.

[15] Mochizuki H, Joh K, Kawame H, Imadachi A, Nozaki H, Ohashi T et al. Mitochondrial encephalomyopaties preceded by De Toni-Debrè-Fanconi syndrome or focal segmental glomerulosclerosis. Clin Nephr 1996; 46: 347-352.

[16] Brockington M, Alesanjari N, Sweeney M, Morgan-Hughes JA, Scaravilli F, Harding AE. Kearns-Sayre syndrome associated with mtDNA deletion or duplication. J Neurol Sci 1995; 131: 78-87.

[17] Welzing L, Von Kleist-Retzow JC, Kribs A, Eifingr F, Huenseler C, Sreeram N. Rapid development of life – threating complete atrio-ventricular block in Kearns-Sayre syndrome. Eur J Pediatr 2008. D 0I 10.1007/s 00431-008-0831-x

[18] Chawla S, Coku J, Forbes T, Kannan S. Kearns-Sayre syndrome presenting as complete heart block. Pediatr Cardiol 2008; 29: 659-662.

[19] Isotani H, Fukumoto Y, Kawamura H, Furukawa K, Ohsawa N, Goto Y et al. Hypoparathyroidism and isulin-dependent diabetes mellitus in a patient with Kearns-Sayre syndrome harbouring a mitochondrial DNA deletion. Clinical Endocrinology 1996; 45: 637-641.

[20] Kurijama M, Suehara M, Marume N, Osame M, Igata A. High CSF lactate and pyruvate content in Kearns-Sayre syndrome. Neurology (Cleveland) 1984; 34: 253-255.

[21] Mohri I, Tanüke M, Fujimura H, Matsuoka T, Inui K, Nagai T, Okada S. A case of Kearns-Sayre syndrome showing a constant proportion of deleted mtDNA in blood cells during 6 years of follow-up. J Neurol Sci 1998; 158: 106-108.

[22] Toppet M, Telerman-Toppet N, Szliwowski HB, Vainsel M, Coers C. Oculocraniosomatic neuromuscular disease with hypoparathyroidism. Amer J Dis Childh 1997; 131: 437-441.

[23] Sanaker PS, Husebye ES, Fondenes O, Bindoff LA. Clinical evolution of Kearns-Sayre syndrome with polyendocrinopathy and respiratory failure. Acta Neurol Scand 2007; 115 (suppl 187): 64-67.

[24] De Sanctis V, Calzolari F, Piazzi A, Berio A. La sindrome di Kearns-Sayre associata con deficit di GH. Ped Med Chirurg 2003; 25: 447-451.