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EPILEPSY AND HYPOTHYROIDISM IN CHILDREN WITH DOWN SYNDROME

EPILEPSIA E HIPOTIREOIDISMO EM CRIANÇAS COM SÍNDROME DE DOWN

EPILEPSIA E HIPOTIROIDISMO EN NIÑOS CON SÍNDROME DE DOWN

Ana Batschauer[1], Paulo Breno Noronha Liberalesso[1,2], Alexandre Menna Barreto[3], Jair Mendes Marques[2], Bianca Simone Zeigelboim[2], Eliana Garzon[4]

ABSTRACT

Objective: This paper presents a review of epilepsy and thyroid dysfunction in children with Down syndrome and analyzes the possible association between these comorbidities. Methods: The medical records of all patients with Down syndrome treated at the Pediatric Neurology Department of Pequeno Príncipe Children's Hospital e from January 2008 to January 2014 (72 patients) were analyzed and divided into two groups: one consisting of patients with Down syndrome and epilepsy (GROUP I), and the other of patients with Down syndrome and without epilepsy (GROUP II). The two groups were then compared with respect to the prevalence of thyroid dysfunction. The association of the mother's age at the child's birth and the presence of epilepsy and/or thyroid dysfunction were also tested. Results: The data showed that among children with Down syndrome there is no significant association (p=0.09) between the presence or absence of epilepsy and the presence or absence of hypothyroidism. In addition, no significant association was found between the mother's age at the child's birth (<35 or ≥35 years) and an increased risk of epilepsy (p=0.37) nor an increased risk of hypothyroidism (p=0.42). Conclusions: Our study found no significant association between the two comorbidities, epilepsy and thyroid dysfunctions, in people with DS, or significant relationship of each one individually with the mother's age at the child's birth in this population.

Keywords: Down syndrome; Thyroid gland; Epilepsy.

RESUMO

Objetivo: Este artigo apresenta uma revisão sobre epilepsia e disfunção tireoidiana em crianças com síndrome de Down e analisa uma possível associação entre estas duas comorbidades. Métodos: Foram analisados todos os prontuários médicos de pacientes com síndrome de Down tratados no Departamento de Neurologia Pediátrica do Hospital Infantil Pequeno Príncipe entre janeiro de 2008 e janeiro de 2014 (72 pacientes), e divididos em dois grupos: um de pacientes com síndrome de Down e epilepsia (GRUPO I) e outro de pacientes com síndrome de Down e sem epilepsia (GRUPO II). Os dois grupos foram comparados quanto à disfunção tireoidiana. A associação entre a idade materna ao nascimento da criança e a presença de epilepsia e/ou disfunção tireoidiana também foi testada. Resultados: Os dados mostram que nas crianças não há associação significativa (p=0,09) entre a presença ou ausência de epilepsia e a presença ou ausência de hipotireoidismo. Além disso, não há associação significativa entre a idade da mãe ao nascimento da criança (< 35 ou ≥ 35 anos) e aumento do risco de epilepsia (0=0,37) nem aumento do risco de hipotireoidismo (p=0,42). Conclusões: Nosso estudo não encontrou associação significativa entre as duas comorbidades, epilepsia e disfunção tireoidiana, em pessoas com síndrome de Down nem relação significativa de cada um individualmente com a idade da mãe ao nascimento da criança nesta população.

Descritores: *Síndrome de Down; Glândula tireoide; Epilepsia.*

RESUMEN

Objetivo: Este artículo presenta una revisión sobre epilepsia y disfunción tiroidea en niños con síndrome de Down y analiza una posible asociación entre estas dos comorbidades. Métodos: Fueron analizados todos los prontuarios médicos de pacientes con síndrome de Down tratados

1. Medical Residency Program in Pediatrics. Pequeno Príncipe Children's Hospital. Curitiba, Paraná, Brazil.
2. Otoneurology Laboratory, Tuiuti University of Paraná. Curitiba, Paraná, Brazil.
3. Pediatric Endocrinology Department, Pequeno Príncipe Children's Hospital. Curitiba, Paraná, Brazil.
4. Electroencephalograghy Section, Neurological Clinic of the Hospital das Clínicas of São Paulo, University of São Paulo Medical School. São Paulo. Brazil.

Correspondence: Paulo Breno Noronha Liberalesso. Hospital Infantil Pequeno Príncipe.
Av. Iguaçu, 1472, Água Verde. CEP: 80250-060. Curitiba, Paraná, Brazil. paulo.neuroped@gmail.com

en el Departamento de Neurología Pediátrica del Hospital Infantil Pequeno Príncipe entre enero de 2008 y enero de 2014 (72 pacientes), y divididos en dos grupos: uno con pacientes con síndrome de Down y epilepsia (GRUPO I) y otro con pacientes con síndrome de Down y sin epilepsia (GRUPO II). Los dos grupos fueron comparados cuanto a la disfunción tiroidea. La asociación entre la edad materna en el nacimiento del niño y la presencia de epilepsia y/o disfunción tiroidea también fue probada. Resultados: Los datos muestran que en los niños no hay asociación significativa (p = 0,09) entre la presencia o ausencia de epilepsia y la presencia o ausencia de hipotiroidismo. Además, no hay asociación significativa entre la edad de la madre en el nacimiento del niño (< 35 ó ≥ 35 años) y aumento del riesgo de epilepsia (0=0,37) ni aumento del riesgo de hipotiroidismo (p = 0,42). Conclusiones: Nuestro estudio no encontró asociación significativa entre las dos comorbidades, epilepsia y disfunción tiroidea, en personas con síndrome de Down ni relación significativa de cada uno individualmente con la edad de la madre en el nacimiento del niño en esta población.

Descriptores: *Síndrome de Down; Glándula tiroides; Epilepsia.*

INTRODUCTION

Down's syndrome (DS) was described originally in 1866 by British physician John Langdon Down. It is considered the most frequent and well known chromosomal abnormality, with an incidence varying according to maternal age from 1:2000 live births at the beginning of the fertile life to 1:40 in pregnant women over 40 years.[1,2] Most cases are caused by a mechanism of non-disjunction leading to trisomy 21, although cases of on unbalanced translocation involving chromosome 21 and some other chromosome, and mosaicism may occur.[2,3]

A major cause of mental retardation of prenatal origin, DS often has several associated comorbidities, including: congenital heart defects, such as ventricular septal defect, atrioventricular canal defect and patent ductus arteriosus; problems with the gastrointestinal tract, such as duodenal atresia and aganglionar bowel disease; hearing problems; vision problems, such as cataracts, strabismus and refractive optical defects; early degeneration of the musculoskeletal system, with atlanto-axial subluxation and collapse of vertebral bodies; endocrine diseases, such as diabetes and thyroid dysfunction (hypothyroidism or hyperthyroidism); leukemias and solid tumors; immunological changes; neurological problems, such as epilepsy and early-onset dementia of the Alzheimer type; obesity and premature aging. These conditions may pose hazards to health of these children and shorter survival.[2,4-6]

Epilepsy and thyroid dysfunction stand out among the comorbidities previously mentioned, because of their high prevalence and serious health repercussions in the affected individuals. Although seizures are not present among the clinical findings in the original description of the syndrome, it is currently known that they are significantly more frequent in children with DS than in the general population, and less frequent than in patients with mental disabilities related to other etiologies.[1,2,5]

Given the findings of the last decade in relation to the significant percentage of children with DS and epilepsy (approximately 1 in 10), it is clear that physicians should suspect the possibility of epilepsy and intervene as early as possible when seizures are suspected, to maximize the patient´s development and improve quality of life as much as possible.[5]

Involuntarily, the association between DS and thyroid dysfunction was first proposed in 1866 by Seguin, who described the condition as "furfuraceus" cretinism, in an attempt to differentiate it from that of "stable" cretins. At the turn of the twentieth century, Bournville (1903) described the pathological association between DS and thyroid dysfunction, which was soon followed by clinical and histopathologic confirmation. However, the first case report of a person with DS and clinical hyperthyroidism was realized by Gilchrist (1946), and of a person with DS and hypothyroidism, by Maranon (1951). At the turn of the third millennium, thyroid dysfunction in people with DS continues to be the focus of ongoing interest and research.[3]

A review of literature on the subject shows that 3 to 54% of people with DS have biochemical evidence of hypothyroidism, with increased lifetime prevalence. Both hypothyroidism and hyperthyroidism are more common in people with DS than in the general population.[3,7,8]

The recognition of thyroid dysfunction may be rather difficult in people with DS, taking into consideration that clinical symptoms and signs of both conditions overlap in several respects. Either hypothyroidism or DS may present, for example, hypotonia, lethargy, dullness, mental retardation, growth failure, prolonged neonatal jaundice, delayed closure fontanellae, macroglossia, obesity etc.[3,7,9] The delay in the diagnosis of hypothyroidism leads to an aggravation of the already fragil health situation of this population.[9]

There are several reports of people with DS and thyroid dysfunction in association with other clinical conditions. Regarding thyroid dysfunction and epilepsy, yet little is known about their coexistence and relation with each other in this population.

This paper aims to explore this issue. It presents a review of epilepsy and thyroid dysfunction in children with DS and analyzes the possible association between these comorbidities in this population, also evaluating the influence of the mother's age at the child's birth regarding development with these clinical conditions.

METHODS

The study is observational and cross-sectional. Medical records of all patients with DS treated at the Pediatric Neurology Department of Pequeno Príncipe Children's Hospital from January 2008 to January 2014 were analyzed, totaling 72 patients. The only criteria for inclusion in the study were the presence of DS and the fact of being accompanied at the health service and within the period of time aforementioned. The patients participating in this study had no financial outlay.

The data collected included the following variables: sex, age, presence or absence of epilepsy, age at first seizure, epilepsy classification, the first electroencephalogram (EEG), cranial tomography (CT), magnetic resonance imaging (MRI), thyroid function (normal, hypothyroidism or hyperthyroidism) and the mother's age at the child's birth. All EEG were performed with a minimum duration of 30 minutes, and with electrodes positioned according to the International 10-20 System (an internationally recognized method to describe the location of scalp electrodes), in digital EEG monitoring equipments with 21 channels (Nihon Koden®, Neurotec® and Neurovirtual

Brain Wave II®). For analysis of thyroid hormones, normal reference values were considered: free thyroxine fraction (free-T4) – 0.8 a 1.75 ng/dl and thyroid-stimulating hormone (TSH) – 0.6 a 6.30 UI/ml.

After data collection, patients were divided into two groups, one consisting of patients with DS and epilepsy (*GROUP I*), and the other of patients with DS and without epilepsy (*GROUP II*), and then each group was compared to the other with respect to the prevalence of thyroid dysfunction (hypothyroidism or hyperthyroidism). The influence of the mother's age at the child's birth with regard to the presence of epilepsy and/or thyroid dysfunction was also tested. Data analysis used the methodology of descriptive statistics and Chi-square test at a significance level of 0.05. The research protocol was approved by the Ethics Committee on Research Involving Human Subjects (registration number CEP 725.489/2014) at Pequeno Príncipe Children's Hospital.

RESULTS

Seventy-two patients with DS were included in the study and divided into two groups for analysis and comparison: *GROUP I* - patients with DS and epilepsy and *GROUP II* – patients with DS and without epilepsy.

GROUP I: 34 patients, 18 (52.94%) male and 16 (47.06%) female, aged between 20-88 months (mean 53.85 ± 21.59 months). The age at first seizure ranged from 3-53 months (mean 29.35 ± 20.60 months). The types of epilepsy were classified as West syndrome (5/14.70%), focal epilepsy (15/44.12%), multifocal epilepsy (4/11.76%) and generalized epilepsy (10/29.41%). The detailed classification of epilepsies and results of EEGs records are in Table 1. All patients performed CT examination, 21 (61.76%) normal, 10 (29.41%) brain atrophy, 1 (2.94%) left parietal gliosis, 1 (2.94%) left frontocentral gliosis and 1 (2.94%) left temporal gliosis. Eighteen patients were submitted to brain MRI, 9 (50%) normal, 4 (22.22%) cerebral atrophy, 2 (11.11%) cerebral atrophy and periventricular leukomalacia, 1 (5.55%) left parietal gliosis, 1 (5.55%) frontocentral and parietal gliosis and 1 (5.55%) left centrotemporal gliosis. Regarding the evaluation of thyroid function, 23 (67.65%) normal and 11 (32.35%) hypothyroidism. Mother's age at the child's birth ranged from 24-42 years (mean 33.94 ± 4.96 years).

GROUP II: 38 patients, 19 (50%) male and 19 (50%) female, aged between 18-95 months (mean 53.87 ± 20.53 months). Regarding the evaluation of thyroid function, 32 (84.21%) normal and 6 (15.79%) hypothyroidism. Mother's age at the child's birth ranged from 26-42 years (mean 34.29 ± 4.80 years).

GROUP I and GROUP II: with the use of Chi-square test at a significance level of 0.05, it was found that in children with DS there is no significant association (p=0.09) between the presence or absence of epilepsy and the presence or absence of hypothyroidism (Table 2), and there is also no significant association (p=0.37) between the mother's age the child's birth (<35 or ≥ 35 years) and the increased risk of epilepsy (p=0.37) (Table 3) and between the mother's age at the child's birth (<35 or ≥ 35 years) and the increased risk of hypothyroidism (p=0.42). (Table 4)

Table 1. Classification of epilepsies and EEGs records.

Patients	Classification of Epilepsies	EEGs records
1	Focal	BA-DD. SW - right frontocentral
2	West syndrome	BA-MD - hypsarrhythmia
3	West syndrome	BA-MD - hypsarrhythmia
4	Focal	BA-DD. SW - left frontocentral
5	Focal	BA-DD. SW - rigth frontal
6	Generalized	BA-DD. S, SW, PSW - generalized discharges
7	West syndrome	BA-MD - hypsarrhythmia
8	Focal	BA-DD. SW - right temporal
9	Generalized	BA-MD. S, SW, PSW - generalized discharges
10	Generalized	BA-MD. PSW - generalized discharges
11	Multifocal	BA-MD. SW - multifocal
12	Focal	BA-DD. SW - right parietal and occipital
13	Multifocal	BA-MD. SW - multifocal
14	Generalized	BA-MD. PSW - generalized discharges
15	Focal	BA-DD. SW - right frontal and parietal
16	Generalized	BA-DD. S, SW - generalized discharges
17	West syndrome	BA-MD - hypsarrhythmia
18	West syndrome	BA-MD - hypsarrhythmia
19	Focal	BA-MD. SW - right parietal and occipital
20	Multifocal	BA-MD. SW - multifocal
21	Generalized	BA-MD. S, SW, PSW - generalized discharges
22	Focal	BA-DD. SW - left central and parietal
23	Generalized	BA-MD. S - generalized discharges
24	Focal	BA-DD. SW - left parietal and occipital
25	Focal	BA-DD. SW- left central and parietal
26	Multifocal	BA-MD. SW - multifocal
27	Focal	BA-DD. SW - right central and parietal
28	Generalized	BA-MD. S - generalized discharges
29	Focal	BA-DD. SW - left frontal and central
30	Generalized	BA-DD. S - generalized discharges
31	Focal	BA-DD. SW - left parietal and occipital
32	Focal	BA-MD. SW - right parietal and occipital
33	Focal	BA-MD. SW - left temporal and parietal
34	Generalized	BA-DD. S - generalized discharges

Background activity - BA. Sharp wave discharges - SW. Discreetly disorganized - DD. Moderate disorganized - MD. Spike - S. Spike-wave - SW. Polispike-wave - PSW.

Table 2. Relationship between hypothyroidism and epilepsy.

	Hypothyroidism		Total
	Yes	No	
With epilepsy	11	23	34
Without epilepsy	6	32	38
Total	17	55	72

Significance level (p=0.09).

Table 3. Relationship between the mother's age at the child's birth and risk of epilepsy.

	Mother's age		Total
	under 35 years	35 years and over	
With epilepsy	17	17	34
Without epilepsy	15	23	38
Total	32	40	72

Significance level (p=0.37).

Table 4. Relationship between the mother's age at the child's birth and risk of hypothyroidism.

	Mother's age		Total
	Under 35 years	35 years and over	
Hypothyroidism	9	8	17
Normal	23	32	55
Total	32	40	72

Significance level (p=0.42).

DISCUSSION

Patients with DS often have comorbidities, among which stand out, because of their prevalence and serious repercussions on health situation, epilepsy and thyroid dysfunction. It is known that epilepsy is significantly more frequent in children with DS than in the general population and less frequent than in patients with mental disabilities related to other etiologies.[1,2,5,10]

The age of onset of seizures in people with DS is variable, with bimodal distribution with a first peak incidence in the first two decades of life, especially before one year of age, and a second peak starting from the third decade of life, especially in the fifth and sixth decades of life.[2,5,10] The prevalence of epilepsy increases with age, reaching 46% in those over 50 years.[5]

In our research, the age of onset of seizures ranged from 3 to 53 months (mean 29.35 months ± 20.60 months).

Boys tend to have earlier onset of seizures. This may reflect the male predominance in the group of infantile spasms, which usually occur in the first year of life[5]. The late onset of seizures is associated with increased susceptibility for the development of dementia of the Alzheimer type.[5,11]

Two aspects are relevant to explain the higher incidence of epilepsy in patients with DS: presence of other diseases or pathological conditions related to increased risk of seizures; structural and functional changes in the brain resulting from the syndrome itself. [2,5,10]

In relation to diseases or pathological conditions related to increased risk of seizures, a study demonstrated that 61.7% had definite or presumed etiology, including heart disease (hypoxia crises and arterial occlusion by thrombosis), perinatal complications at birth (bleeding and choking) and infections (febrile seizures, infections of the central nervous system and brain abscess).[5]

With respect to the structural and functional changes that may be present in the brain of patients with DS and influence the presence of seizures, we mention the lower number of GABAergic neurons in the cerebral cortex, abnormalities in calcium ion channels, changes in neurotransmitters (for example, the serotonin, an inhibitory neurotransmitter in various regions of the brain, which is present at lower levels in these people), lower neuronal density in the hippocampal, dendritic malformation, degeneration of pyramidal and extrapyramidal neurons, abnormal lamination of the cerebral cortex and abnormalities in synaptic transmission.[2,5,10]

Genetic factors may also influence the presence of seizures in DS, as the gene of progressive myoclonic epilepsy of Unverricht -Lundborg type and the gene determining subunit of glutamate receptors, both located on chromosome 21.[2,11]

All types of seizures may occur in patients with DS, although certain types are more frequent, with approximately 47% of patients developing partial seizures, 32% infantile spasms and 21% generalized tonic-clonic seizures. At younger ages, the most common types of seizures are infantile spasms and generalized tonic-clonic seizures, while at older ages, simple partial seizures, complex partial seizures and generalized tonic-clonic seizures.[2,5,10,11]

The classification of epilepsy among the patients with DS and epilepsy participating in this study (*GROUP I*) was the following: 5(14.7%) West syndrome (WS), 15(44.1%) focal epilepsy, 4(11.7%) multifocal epilepsy and 10(29.4%) generalized epilepsy. Our data are similar to those of other authors, with a predominance of focal epilepsies in children with DS.

However, our incidence of WS is lower than in other researches. The relationship between DS and infantile spasms does not seem to be merely casual, given the high number of reports of this association.[2,12,13] Other types of seizures reported in patients with DS are myoclonic seizures and the reflex epilepsies, more frequent in this group of people than in the general population.[2]

The EEG is a very useful method in the diagnosis and management of epilepsy[1]. Following the pattern of incidence of epilepsy described above, the incidence of electroencephalographic abnormalities in individuals with DS is significantly higher than in the general population, and lower than in other groups of patients with mental disabilities. Despite numerous studies on the subject, is not yet recognized a specific EEG pattern of the syndrome.[1,5]

Electroencephalographic abnormalities already described in people with DS are the following: spike, spike-wave complexes and polispike wave[1]. The detailed classification of epilepsy and EEG findings of patients participating in the study can be seen in Table 1.

In relation to thyroid dysfunction, its importance is clearly shown in the scientific literature about the subject, which demonstrates that 3-54% of these individuals have biochemical evidence of hypothyroidism with increased lifetime prevalence. Both hypothyroidism and hyperthyroidism are more common in people with DS than in the general population.[3,7,8]

Thyroid dysfunction in DS can be congenital or acquired, compensated (subclinical) or decompensated, transient or persistent, with hypothyroidism or hyperthyroidism.[3,9]

The most common form of thyroid dysfunction in these patients is transient subclinical hypothyroidism, which is characterized by slightly elevated levels of thyroid stimulating hormone (TSH) and normal levels of free-thyroxine (free-T4), with spontaneous lifetime recovery.[3,8,9]

Congenital hypothyroidism is up to 28 times more frequent in children with DS than in the general population.[3,7-9] This finding suggests that there may be genes on chromosome 21 involved in the development of the thyroid.[7,8] Some mechanisms proposed to explain thyroid dysfunction in these children are: thyroid relatively small (hypoplastic) in relation to age and the increased metabolic demands accompanying the body growth; dysfunction in the hypothalamic-pituitary-thyroid axis, delay in its maturation or slowness of response to TSH.[7-9,14,15] The acquired hypothyroidism is usually associated with the presence of antithyroid antibodies, suggesting an autoimmune etiology, being common occurrence from the age of 8 years, with an increase in incidence with advancing age.[3,9] It is known that the population with DS has increased prevalence of autoimmune diseases affecting both endocrine and non-endocrine organs, and the most common are those related to the thyroid gland, such as Hashimoto's thyroiditis. The antithyroid antibodies, Thyroid Peroxidase antibodies and Thyroglobulin antibodies are found in 13-34% of patients with DS, which may have normal thyroid function or have hypothyroidism or hyperthyroidism.[3,7]

It should be noticed that the clinical manifestations of DS in its natural course and hypothyroidism overlap in several aspects. For example, both may present hypotonia, lethargy, dullness, mental retardation, growth failure, prolonged jaundice neonatal, delayed closure of fontanellae, macroglossia, obesity etc.[3,7,9] Because of this, delay in diagnosis of hypothyroidism can occur in these people, leading to a deterioration in their health.[9]

The additive effects of DS and hypothyroidism undoubtedly can lead to amplification of health problems in this population.[9] An important example is growth failure.[7] Karlsson et al.[7] in their longitudinal study involving 85 children with DS demonstrated that the growth rate of children with DS and hypothyroidism is significantly lower than the growth rate of children with DS without hypothyroidism, with a significant improvement in this parameter after one year of treatment with levothyroxine.

Studies have found that even subclinical hypothyroidism can lead to the emergence of significant sequelae such as anemia, hypotonia and cognitive and growth deficits. Treatment with thyroid hormone replacement should be encouraged even in cases of subclinical hypothyroidism in view of the ease of its implementation in practice, virtually no adverse effects, and benefits in preventing the development of the aforementioned sequels and the evolution to a state of overt hypothyroidism.[3,7,8]

Hyperthyroidism is found less frequently than hypothyroidism in DS, without gender predominance. Its congenital form is rare, but its negative impacts on fetal and postnatal development require a more careful look at this condition.[9,16,17] In our study no cases of children with DS and hyperthyroidism were found.

There are several protocols for monitoring of thyroid hormones in patients with DS. Many authors suggest that patients with DS and normal thyroid function should be monitored annually, and those with subclinical hypothyroidism, every three months.[9]

In scientific literature, there are several reports of people with DS and thyroid dysfunction in association with other clinical conditions.[3] To date an association has been found between cases of DS and thyroid dysfunction with early puberty and diabetes *mellitus*.[3] In relation to thyroid dysfunction and epilepsy, despite its considerable prevalence and impact on health status of patients with DS, little is yet known.

It is well known that there is reciprocal influence between epilepsy and neuroendocrine system in the body. Hormonal changes may alter the excitability of neurons in the central nervous system (CNS), increasing the frequency of epileptic episodes and, on the other hand, these can alter the functioning of the neuroendocrine system, particularly the hypothalamus and pituitary. Studies in patients with epilepsy confirm that epileptic seizures alter circulating levels of endocrine hormones such as prolactin, luteinizing hormone (LH) and growth hormone (GH).[18]

In our study, in the group of children with DS and epilepsy, 67.65% patients were normal in relation to thyroid function and 32.35% had hypothyroidism, and no cases of hyperthyroidism were found. On the other hand, in the group of children with DS and without epilepsy, 84.21% were normal in relation to thyroid function and 15.8% had hypothyroidism, and no cases of hyperthyroidism were found. The statistical analysis shows no significant difference between the presence or absence of epilepsy and the presence or absence of hypothyroidism, and also no significant association between the mother's age at the child's birth and the increased risk of epilepsy and between the mother's age at the child's birth and the increased risk of hypothyroidism.

CONCLUSIONS

Therefore, our study found no significant association between the two comorbidities, epilepsy and thyroid dysfunctions, in people with DS, or significant relationship of each one individually with the mother's age at the child's birth in this population. This study aimed to contribute to the understanding of DS and its comorbidities, with focus on epilepsy and thyroid dysfunction. Although we found no association between these comorbidities in patients with DS, we emphasize to health professionals who deal with these people about the importance of early diagnosis and appropriate treatment of the comorbidities, so that this population has better health and quality of life. More studies are needed to elucidate the issues raised in this paper.

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