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Summary

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Editorial

Esta edição do JECN aborda aspectos relacionados ao estigma, depressão e autismo. Os dados apresentados por Lunardi e colaboradores mostram que os profissionais da educação têm um conhecimento parcial sobre epilepsia e que um curso de curta duração foi capaz de aumentar o conhecimento e reduzir o estigma nesta população. Este tipo de abordagem é fundamental para reduzir a lacuna de tratamento e melhorar a qualidade de vida das pessoas com epilepsia.

O trabalho de Salgado et al., confirma a opinião generalizada de que a depressão é comum nas pessoas com epilepsia e mostra a associação da depressão com alguns fatores sociodemográficos bem como a relação entre sintomas depressivos e controle de crises antes e depois do tratamento cirúrgico em pacientes com crises refratárias ao tratamento medicamentoso.

Pereira et al. discute em um artigo de revisão que o autismo é associado com epilepsia na infância em quase 30% das crianças, sugerindo que as duas condições apresentam mecanismos fisiopatológicos semelhantes.

Fernando Cendes
Editor, JECN

Message of the President of the Brazilian League of Epilepsy

Prezados colegas,

Dentro do espírito solidário e compartilhador que de certa (e bem vinda) forma permeia os recentes encontros de sociedades médicas, a Liga Brasileira de Epilepsia inclui oficialmente em seu calendário de atividades científicas participações no IX Congresso Brasileiro do Cérebro Comportamento e Emoções (São Paulo, 26 a 29 de junho, 2013) e no XXIV Congresso da Sociedade Brasileira de Neurofisiologia Clínica (a ser sediado no Rio de Janeiro, 04 a 06 de setembro, 2013). Estes representativos eventos científicos nacionais terão em suas vindouras edições espaços dedicados a discussão e atualização no diagnóstico, tratamento e situações comórbidas associadas à epilepsia. Igualmente interessante na área de educação médica continuada é a manutenção e aprimoramento de parcerias da LBE com a indústria farmacêutica, promovendo cursos de cunho itinerante e formação de replicadores, de forma ética e estruturada, absolutamente sob a égide da LBE. Datas e locais dos referidos cursos, com planejamento em 2013, serão anunciados oportunamente. Ainda para o início do ano de 2013 é prevista reunião entre a LBE, também responsável pelo Departamento Científico da Academia Brasileira de Epilepsia e a Coordenação dos referidos departamentos, visando a organização de ações de divulgação e esclarecimento a população sobre a experiência de (con)viver com epilepsia. Com estas e outras iniciativas de cunho científico e social esperamos solidificar e mesmo ampliar o papel já histórico de nossa sociedade médica.

Atenciosamente,

Luciano De Paola
Presidente da Liga Brasileira de Epilepsia
Gestão 2012-2014

Original Article

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Epilepsy Perception Amongst Education Professionals

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ABSTRACT

Introduction: Epilepsy is a prevalent neurological disorder that may cause school failure due to several factors such as seizure severity, lack of information about the condition and stigma. This study aimed to evaluate the degree of perceived stigma and knowledge towards epilepsy among education professionals, and additionally, provide them correct information about epilepsy to reduce stigma through a training course. **Methods:** Social and demographic data, as well as the degree of stigma were obtained through the Stigma Scale of Epilepsy. To estimate the level of educational professionals' knowledge about epilepsy we used the Questionnaire about Epilepsy. Statistical analysis consisted of Pearson's or Spearman's correlation tests for numerical parametric or non-parametric variables were used to determine potential significant associations. A $p < 0.05$ was considered significant. **Results:** Two hundred and twenty-five education professionals were interviewed in three different cities in Southern Brazil. Approximately 65% of subjects would attempt to open the mouth of a student during a seizure and the stigma measured by Stigma Scale of Epilepsy before the course was 45.4 ± 16.61. **Conclusion:** The data indicate that education professionals have partial knowledge about epilepsy and a short duration course would be able to improve it and reduce its stigma in this population.

Keywords: epilepsy education, stigma, education professionals, Questionnaire about Epilepsy, Stigma Scale of Epilepsy.

RESUMO

Percepção de epilepsia entre profissionais da educação

Introdução: A epilepsia é uma doença neurológica prevalente que pode causar fracasso escolar devido a fatores como severidade das crises, pouca informação sobre a doença e estigma. Este estudo teve como objetivo avaliar a percepção do estigma e conhecimento em epilepsia pelos profissionais de educação, fornecer informações corretas sobre epilepsia e reduzir o estigma através de um curso de curta duração. **Metodologia:** Os dados sociodemográficos e o grau de estigma foram obtidos através da Escala de Estigma em Epilepsia. O grau de conhecimento em epilepsia foi obtido através da adaptação do Questionário Sobre Epilepsia. O teste de correlação de Pearson ou Spearman foi utilizado para análise das variáveis numéricas contínuas paramétricas ou não-paramétricas. O valor de $p<0,05$ foi considerado significante. **Resultados:** Duzentos e vinte e cinco sujeitos foram entrevistados em três cidades do Sul do Brasil. Aproximadamente 65% deles abriria a boca do estudante durante uma crise e o grau do estigma avaliado com a Escala de Estigma em Epilepsia pré-curso foi de 45.4 ± 16.61. **Conclusão:** Os dados indicam que os profissionais da educação têm um conhecimento pacial sobre epilepsia e que um curso de curta duração foi capaz de aumentar o conhecimento e reduzir o estigma na população estudada.

Palavras-chave: educação em epilepsia, profissionais da educação, Questionário sobre Epilepsia, Escala de Estigma em Epilepsia.

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INTRODUCTION

Most people with epilepsy have their first seizure before the age of 20, and it can affect their development. According to Souza and cols. (2002),[1] the diagnosis of epilepsy as a neurological condition, brings a series of burdens to the patient and his family, affecting their behavior and well-being. Being diagnosed with epilepsy activates a whole system of beliefs in personal and social levels that could potentially modify behavior towards oneself and society. Furthermore, it involves individual perceptions and expectations related to the life history of each affected person in different ways.

Epilepsy is the most common chronic neurological disorder in childhood, affecting approximately 3.6-5.3 children per 1000.[2] There is evidence of association between epilepsy and specific learning disabilities[3]. The difficulties presented by children with epilepsy may be related to epilepsy itself and also to variables involved with the schooling process such as: low expectations from parents and teachers about their success, rejection from teachers and schoolmates and low self-esteem.[4] Moreover, ignorance and stigma about the disease can also interfere with school attendance.[5] The starting point for any discussion related to stigma must be Goffman's[6] definition as "*an attribute that is deeply discrediting*".[7] Goffman asserted that an individual who is stigmatized possesses "*a trait that can obtrude itself upon attention and turn those of us whom he meets away from him, breaking the claim his other attributes have on us*".[7]

It is crucial to provide knowledge about epilepsy and its care right after its diagnosis – regardless of the subject's age. Specific challenges include gaining control over such a chronic condition, often difficult to predict, and the stigma frequently associated. Therefore, education on epilepsy is extremely important. Children spend most time at school and the contribution of the education professionals in health education is essential. They are part of the social network of students with epilepsy, and, when well targeted, they will be more able to deal with adverse situations and unforeseen seizures at school environment. The educator is an important element in providing correct and non-biased information on several issues, including the health area.[8]

The aim of this study was to evaluate the level of knowledge and perception of the magnitude of stigma on epilepsy among basic education professionals before and after the attending to an educational course on epilepsy. This study will allow the development of more effective interventions regarding epilepsy education aiming to improve the psychosocial health of students with epilepsy. Although education professionals are able to confront these situations, there are few undergraduate programs that include courses on Inclusive Education, particularly on epilepsy, in Brazil.

METHODS

To estimate the level of educational professionals' knowledge about epilepsy we used the Questionnaire about Epilepsy (QAE), developed by *Associação Brasileira de Epilepsia* (ABE).[9,10] The questionnaire contains 35 statements concerning the following topics: A – Concepts and definition of epilepsy and its causes (10 items); B – Treatment and adverse effects of antiepileptic medication (10); C – Popular stigma about epilepsy (5); D – Activities of people with epilepsy (PWE) (5); E – First-aid during and after an epileptic seizure (5). Respondents were asked to indicate whether the statements were correct or wrong. Two more issues were added to the questionnaire, one on the topic "Activities of people with epilepsy" that is "People with epilepsy should attend special education" and another one on the topic "Treatment and medication adverse events" – "Epilepsy usually improves with religious or spiritual interventions". Additionally, it was added the option "I do not know" as a possible answer.

To determine the perception of stigma in epilepsy we used the Stigma Scale of Epilepsy (SSE).[11] This scale contains five questions with twenty-four items, each with a four-point scale: the individuals were asked to indicate the most appropriate answer for that item, marking the number corresponding to the category (1=not at all; 2=a little; 3=a lot; 4=totally); with the highest score of 100 indicating maximum stigma.

The questionnaire and the SSE were presented to education professionals in phase 1, before the 4-hour duration course "Epilepsy and Education", given by the researchers (MSL and FPSS). The course was given through a classical live class, based on pedagogical implications of Ausubel's Meaningful Learning Theory[12] and its metacognitive tools, the Conceptual Maps,[13] to enable the meaningful learning and retaining of knowledge for more prolonged time. A group of 32 education professionals was assessed twice: before the epilepsy lecture and one month afterwards, with the aim of measuring its efficacy.

The primary objective was to measure the education professionals' knowledge about epilepsy and to estimate their level of stigma on epilepsy. The hypothesis is that after the course the knowledge on epilepsy would improve, and the level of perceived stigma decrease, measured by QAE and SSE.

The collected data were stored and analyzed with SPSS for Windows, Standard Version 17.0 (SPSS Inc., Chicago, IL, USA). After descriptive analysis of the socio-demographic variables, univariate statistical analysis consisted of Pearson's or Spearman's correlation tests for numerical parametric or non-parametric variables respectively were used to determine potential significant associations. The paired Student's *t* test was used to

evaluate the results of SSE pre and post-course. A $p<0.05$ was considered significant.

The study was conducted according to Declaration of Helsinki, Institutional Ethics Committee approved the study and all subjects gave their informed consent before being interviewed.

RESULTS

This study evaluated 225 subjects. Their socio-demographic data (sex, age, educational degree, period employed in education and religion are discriminated in Tables 1 and 2.

Table 1 – Subjects evaluated in the study.

	Frequency	Percentage (%)
Teacher	97	43.1
Undergraduate student	67	29.8
Pedagogue	14	6.2
School administrative technician	41	18.2
Psychologist	3	1.3
Librarian	3	1,3

Table 2 – Subjects' demographic data.

Gender	
Men	79 (35.1%)
Women	146 (64.9%)
Age (years)	31.79±10.63 (18-60)*
Schooling (years)	14.49±2.60 (11-19)*
Time in education profession	10.00±9.27 (0-40)*
Religion[a]	120 (63.2%)
Catholic	9 (4.7%)
Spiritist	25 (13.2%)
Evangelical	9 (4.7%)
Other	27 (14.2%)
No religion	[a] Undeclared=35
Know someone with epilepsy	105 (46.7%)

* mean ± standard deviation (minimum and maximum).

QAE and SSE applied prior to the epilepsy course

Concerning the subject "Concepts, definitions and causes of epilepsy" there were more than 50% of correct answers. However, less than 50% of respondents were able to answer whether or not foods cause epilepsy and only 41.3% knew how to differentiate epilepsy from seizures. Most individuals answered correctly in the field "Treatment and medication adverse events". Few exceptions were the questions "If the person feel any side effect, the antiepileptic drug should be interrupted immediately" in which only 46.7% agreed and only 12.4% of respondents knew about the existence of epilepsy surgery offered by Brazilian public health care system. It is noteworthy that 24.2% of respondents did not know whether epilepsy may be treated by religious or spiritual interventions. Within the field "Stigma and popular knowledge about epilepsy" 51.1% of education professionals answered that nervousness can cause epilepsy and 42.75% of them did not know whether emotional trauma could cause epilepsy. Within the topic "Activities of people with epilepsy", only 42.7% of respondents knew that the person with epilepsy may have learning problems when epilepsy therapy is not appropriate. The majority, 43.1%, could not tell whether the person with epilepsy can drive. On the topic "First Aid during and after seizures" 65.3% of individuals would open the mouth of a person during a seizure in order to avoid tongue bites. Additionally, there was a general lack of knowledge about when it is necessary to refer a patient to the emergency department after a seizure.

The majority of professionals, 120 (53.3%), did not know any person with epilepsy and SSE mean score before the epilepsy course was 45.38±16.61 (minimum and maximum=8-86).

Furthermore, the older the professional, the lower the SSE score obtained ($r=-0.03$, $p<0.01$), as occurred when comparing length of employment in educational field with SSE ($r=-0.11$, $p<0.01$). More years of schooling resulted in lower scores on SSE ($r=0.02$, $p<0.01$). Participants who did not know anyone with epilepsy had a higher perception of stigma in epilepsy [Mean (M)=46.71; Standard deviation (SD)=16.23] than those who knew someone (M=43.74; SD=17.02). However, this difference was not significant at $t(188)=1.22$; $p=-0.089$.

Among the professions involved with education, the highest degree of stigma was found among Librarians [53.33±9.82 (34-66)], followed by Pedagogues [52.20±5.96 (26-86)], School Administrative Technicians [49.76±2.85 (20-84)], Undergraduate Students [43.85±1.82 (11-80)] and Teachers [43.41±2.04 (8-84)], while Psychologists demonstrated the most tolerant scoring average [32.67± 1.33 (30-34)].

Among different religious beliefs, the highest degree of stigma was recorded among Spiritualists 48.67±6.17 (25-79), while others presented SSE scores in decreasing order of intensity: 47.74±3.27 non-religious declared (20-86), Catholics 44.73±1.4 (8-84) and Evangelicals 44.72±3.75 (16-86).

QAE and SSE applied after the epilepsy course

The QAE and SSE were reapplied on 32 subjects after the epilepsy course to evaluate the acquisition of knowledge and eventual changes in perceived stigma. There was an increase in the level of epilepsy knowledge, evidenced by increased correct answers in all fields. It was still observed doubts concerning etiology of epilepsy, since only 40.6% of respondents agreed that "Any brain injury may lead to epilepsy". With respect to stigma and

popular knowledge about epilepsy, 50.0% of respondents agreed that nervousness could cause epilepsy, and only 31.3% answered that this question was wrong. Similarly, only 46% answered that emotional trauma does not cause epilepsy. It is noteworthy to say that the concept that it is necessary to open the patient's mouth in order to avoid tongue bites decreased after the course, since 75% of respondents considered it a erroneous measure of relief to seizures.

The mean score of SSE after the course decreased to 37.38±13.41 (8-59), and it was statistically significant [$t(31)=-3.361$, $p<0,01$, $r=0.52$]. The epilepsy course caused a significant reduction in the perceived stigma in this particular population.

DISCUSSION

Epilepsy is the most common neurological condition in children, and may cause an enormous impact on their quality of life and may greatly influence the most distinctive aspects of their lives[14-16]. Several actions can be taken for improving the quality of life and psychosocial health of a person with epilepsy, such as a proper education and a welcoming school environment.

We observed that education professionals have some knowledge about epilepsy. However, there is a high degree of misconceptions regarding appropriate attitudes to be taken towards a person suffering from seizures and regarding its causes.

Previous studies demonstrated that teachers have a good knowledge about epilepsy due to their higher level of education. In Ojinnaka's (2002)[17] study, with 125 teachers, 37.6% of whom had university degree, but without any form of health education specifically for epilepsy, they had 59.2% of correct answers on questions about epilepsy proposed by the author. In Fernandes and cols' (2007)[18] study about the perception of teachers' knowledge about epilepsy, 43% of teachers claimed to have good knowledge about the disease and 20% had little knowledge, and pointed out that the greatest source of information about this condition were journal articles (53%), television (29%) and school (22%).

This study involved a group of education professionals with approximately 14 years of schooling. This finding is relevant because despite having higher educational levels, none of the participants had received any education directed towards epilepsy in their training years (considering more than 50% of accuracy for each proposition in the QAE). The level of knowledge found in our subjects may be considered inappropriate for an education professional, since important issues such as seizure recognition and basic knowledge in epilepsy were associated with a considerable number of errors.

Lack of knowledge about adequate assistance to seizures still persists, only 39.6% of respondents knew that seizures usually start and stop spontaneously, not requiring specific interventions such as calling to the emergency services in every seizure. Also 65.3% of respondents said that during a seizure one should open the mouth of the seizing person in order to prevent mouth injuries. This finding disagrees with the study of Guilhoto et al. (2007)[8] where only 35.71% of teachers would pull the tongue out of a person during a seizure. Perhaps this is due to the fact that in Guilhoto et al. (2007)[8] study, teachers had more teaching time (17.75 years) compared to ours where education professionals presented 10.0 ± 9.27 (0-40) years of profession. Also, in Guilhoto et al. (2007)[8] more than a half (61.53%) of the teachers knew someone with epilepsy, while in our study only 46.7% of education professionals knew someone with epilepsy. According to Bishop et al. (2006)[19] the most important factors related to teachers' knowledge about epilepsy were teaching time experience and the fact that they had taught a student with epilepsy.

One issue of concern was the lack of knowledge regarding different types of epileptic seizures. Only 47.6% of education professionals stated that seizures may originate from different areas of the brain and therefore may have different clinical manifestations, which may contribute to the non-recognition of seizures other than the generalized tonic-clonic ones in the classroom. In this same area, we found lack of knowledge about the origin of epilepsy. Only 13.8% of respondents knew that any neurological damage can lead to epilepsy and only 20.4% knew how to differentiate seizures from epilepsy. Additionaly, we noticed difficulties in distinguishing neurological symptoms and signs from psychiatric or psychological ones. Approximately half (51.1%) of the subjects believed that nervousness can cause epilepsy and 33.3% of them did not know what to answer. Similarly 32.4% felt that emotional trauma can cause epilepsy and 42.75% did not know what to answer.

In the field that is more directly related to education, which are the activities of people with epilepsy, there was a fair amount of correct answers (68.4%) when asked if the young person with epilepsy may practice sports – issue of importance for Physical Education teachers. The number of correct answers concerning that epilepsy is not usually associated with mental retardation was also satisfactory (73.3%). However, only 42.7% of respondents knew that people with epilepsy may have learning problems if they are not receiving correct treatment.

Stigma is a major issue for people with epilepsy and its reduction is the core of several global campaigns for people with epilepsy support[18]. Teachers are important role models or examples for children and therefore have an important influence on their lives[16]. Teachers' attitudes can influence the educational performance of the child,

especially the child with epilepsy.[19] The perceived stigma degree in this population sample, quantified by SSE, was 45.38±16.61 (8-86). The value of the stigma score was slightly lower than the result found among the general community in the validation process of the scale which reached 46±18.22.[11] This difference can be explained by the nature of stigma, which is multifactorial.[20] There was not statistically significant association between perceived stigma and religion, gender, age and years of education or years of experience in education. Stigma is mainly associated with psychosocial variables[21]. People generally judge characteristics and behaviors of others relying on moral beliefs, cognitive processes and previous learning.[22-24]

As recommended in other studies,[8,10] one of the strategies for reducing stigma and erroneous knowledge on epilepsy is continuing education. In our study, after the questionnaires, all education professionals attended a 4 hours course on epilepsy with basic topics about epilepsy, necessary for someone who will deal with students suffering from this condition.

One month after the intervention, 32 teachers were reassessed by the QAE and SSE. The post-course results demonstrated a considerable increase on knowledge about epilepsy (above 50% of correct answers in the propositions) in all fields evaluated by the epilepsy questionnaire. However, it can be seen that consistent doubts about the concepts, definitions and causes of epilepsy still remains. Only 40.6% of respondents agreed to the issue "Any brain injury can lead to epilepsy". In respect to stigma and popular knowledge about epilepsy, only 31.3% of respondents believed that nervousness does not cause epilepsy. Similarly, only 46% believed that emotional trauma does not cause epilepsy. This may be due to cultural difficulties, where there is confusion in determining what is neurological and psychiatric. This subject was extensively discussed during the course, however it seems to exist a strongly retained knowledge and difficult to modify. Another hypothesis is that the current approach used to correct these erroneous knowledge has not fulfilled its role.

An interesting fact is that the concept that is necessary to open the patient's mouth was considered wrong by 75% of respondents. This issue was thoroughly discussed, with the exposure of the right attitude and also a short movie with wrong attitudes. This information confirms that it is essential to teachers to be informed how to support students with seizures appropriately. A teacher can imprudently, during a seizure, adopt disastrous attitudes to the student with epilepsy and also cause a bad impression to other students.

The mean score of SSE after the course was 37.38± 13.41 (8-59), significantly lower than the perceived stigma prior to the course. This result was lower than that found by Fernandes et al (2007d)[25] in a study on the perception of stigma with 1850 subjects in the state of São Paulo, 42±14. A better understanding of stigma may reduce teaches' inappropriate reactions that limit meaningful experiences and the child normal affective-cognitive development.[26]

This study showed that a low cost, short duration course, based on a simple and pedagogically appropriate educational methodology, with scientific information and targeted to a specific audience, increased epilepsy knowledge and reduced the stigma among education professionals. It can contribute to a better care and well being of students with epilepsy and aiming at future psychosocial benefits.

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Screening Symptoms of Depression and Suicidal Ideation in People With Epilepsy Using the Beck Depression Inventory

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ABSTRACT

Objective: To measure the severity of symptoms of depression and suicidal ideation in people with epilepsy (PWE) before and after epilepsy surgery using the Beck Depression Inventory (BDI). We aimed to determine the factors associated to depression in PWE. **Methods:** PWE, regardless of epilepsy type, seizure type, duration or frequency of seizures, and AEDs were investigated. The sample (n=468) was divided into two groups: pre-operatory (n=346) and pos-operatory (n=122). **Results:** Before epilepsy surgery female gender, unemployment and high seizure frequency were associated factors for the occurrence of symptoms of depression. After epilepsy surgery, the only factor associated to high level of depression symptoms was the lack of seizure remission. Suicidal ideation was associated to seizure frequency before and after epilepsy surgery. **Conclusion:** Our results confirm the generally held view that depression is common in PWE and provide further insight to the association of depression with certain socio-demographic and seizure-related factors before and after epilepsy surgery.

Keywords: epilepsy, seizures, depression, suicidal ideation.

RESUMO

Rastreamento de sintomas de depressão e ideação suicida em pessoas com epilepsia usando o inventário de depressão de Beck

Objetivo: Avaliar a gravidade dos sintomas de depressão e ideação suicida em pessoas com epilepsia (PCE), antes e após o tratamento cirúrgico utilizando o Inventário de Depressão de Beck (BDI). Nosso objetivo foi determinar os fatores associados à depressão em PCE. **Métodos:** PCE, independentemente do tipo de epilepsia, tipo de crises, duração ou frequência das crises, e DAEs, foram investigados. Os pacientes (n=468) foram divididos em dois grupos: pré-operatório (n=346) e de pós-operatório (n=122). **Resultados:** Antes do tratamento cirúrgico, o sexo feminino, o desemprego e a alta frequência de crises foram fatores associados à ocorrência de sintomas de depressão. Após a cirurgia de epilepsia, o único fator associado ao alto nível de sintomas de depressão foi a falta de remissão de crises. Ideação suicida foi associada à frequência de crises antes e após a cirurgia de epilepsia. **Conclusão:** Nossos resultados confirmam a opinião generalizada de que a depressão é comum nas PCE e proporcionam mais evidência para a associação de depressão com alguns fatores sócio demográficos e relacionados às crises antes e após o tratamento cirúrgico das epilepsias.

Unitermos: epilepsia, crises epilépticas, depressão, ideação suicida.

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INTRODUCTION

Epilepsy involves a constellation of problems that goes beyond seizures. It produces medical, psychological, economic and social repercussions that interact in several ways and may be devastating for people with epilepsy (PWE).[1]

Depression is the most recurrent psychiatric comorbidity in PWE and the prevalence is higher in PWE when compared to people with other chronic disorders and general population,[2] with a frequency varying from 30%-70%.[3,4] The etiology of depression is multifactorial and results from complex interaction between endogenous, genetic, therapeutic, and environmental aspects.[5] Sociocultural aspects of epilepsy appears also to affect depression.[6-8] Some of the antiepileptic drugs (AEDs) may cause depression.[9] Other factors, such as seizure frequency, degree of seizure freedom and duration of epilepsy, have been shown to considerably contribute to the prevalence of depression among PWE [10]. Depression significantly affects the quality of life of PWE.[11,12] Unfortunately, most PWE are not regularly screened for depression and consequently, are not treated.[13]

There may be many reasons to explain why depression goes unrecognized in PWE. One of these is the lack of efficient screening measures with well established sensitivity and specificity. According to a previous study,[14] the Beck Depression Inventory (BDI) achieves a quite high level of sensitivity to depression with good specificity and without a high level of false-positive errors. They pointed the BDI to be the instrument that most efficiently measures depression in epilepsy in a short time period (patients take about 10 minutes to fulfill the instrument). Other authors[15] also concluded that the BDI has an important ability to identify major depression in epilepsy and that it is the most appropriate instrument to estimate the frequency and severity of a wide range of depressive symptoms in PWE.

The BDI was validated to Portuguese language[16] and cut-off scores have been developed to define the presence of significant depression symptoms in PWE.[14,15] A BDI score of 12 was set as the cut-off point for mild depression, 20 for moderate depression and 36 for severe depression.

The items constituting the BDI have been separated into two subscales. The first, Affective subscale, evaluate the mental aspect of depression (sadness, pessimism, past failure, loss of pleasure, guilt feelings, punishment feelings, self-dislike, self-criticalness, suicidal ideation, crying, agitation, loss of interest, indecisiveness and worthless). The second, the somatic subscale, access vegetative and somatic symptoms (loss of energy, sleep problems, irritability, appetite problems, concentration, fatigue and loss of interest in sex).[17]

Some authors have highlighted the fact that some measures of psychopathology have the problem of presenting a "somatic effect" or bias, due to the somatic content of these items. This results in probable overestimation of level of depression, when patients indicate items on a depression scale as a result of somatic pathology resulting straightforwardly from illness.[14] The somatic items of the BDI, however, do not confound the measurement of depression in neurological patients and evaluate straightforwardly symptoms of depression.[14] Such bias is an important consideration in selecting the instrument to be used in screening symptoms of depression in epilepsy, besides the amount of time that can be dedicated to the patient interview.

The BDI has a specific suicide item (question 9) to screen for suicidal ideation. Suicidal ideation is an ordinary medical word for thoughts about suicide, which may be as detailed as a formulated plan but without the suicidal act itself. Suicidal ideation seems to be an important indicator for identifying patients at risk of suicide[18] and suicide attempts.[19,20] Although most people who have suicidal ideation do not commit suicide, it may be an important warning sign for suicide attempts, especially in high-risk populations such as PWE.[21-24] Therefore, the identification of risk factors for suicidal ideation may be critical for preventing PWE from committing or attempting suicide.

We measured the severity of symptoms of depression and suicidal ideation in PWE before and after epilepsy surgery using the BDI. We aimed to determine the factors (socio-demographic and seizure-related factors) associated to depression in PWE. Since some of the variables studied are treatable, they could thereby lessen the risk of depression and suicidal risk in epilepsy.

METHODS

Adult individuals with a diagnosis of epilepsy (n=468), regardless of epilepsy type, seizure type, duration or frequency of seizures, and anti-epileptic drugs (AEDs) were randomly recruited through the outpatient clinic of epilepsy of the University of Campinas (UNICAMP) from 2003 to 2010.

Inclusion criteria included epilepsy diagnosis for over two years and age between 17-80 years old. Exclusion criteria included patients with severe medical disorders, progressive neurological disorders, evident mental retardation or alcohol or drug abuse.

At enrollment, all patients provided informed consent to participate in the study and completed the BDI[16] to capture current depressive symptoms. Suicidal ideation was evaluated through the item 9 of the BDI, which evaluates suicide ideation and attempts.

Socio-demographic and seizure-related factors were collected by interview and from information given in the

patient's medical files. Socio-demographic factors included age, gender, education, employment, and civil status. Seizure-related factors included seizure type, epilepsy syndrome, age at onset, duration of epilepsy, seizure frequency, seizure control (at least six months without a seizure) and number of AEDs.

The patients (n=468) were divided into two groups. The patients who were being evaluated for epilepsy surgery comprised 346 patients (pre-operatory group) and the other group, formed by patients who underwent epilepsy surgery comprised 122 patients (pos-operatory group). Because it is a retrospective study, there is some missing data in both groups, which was corrected in the statistical analysis. Table 1 summarizes the socio-demographic and seizure-related characteristics of the study sample.

Statistical analysis

Descriptive statistics are presented in terms of counts, percentages, and mean±standard deviation values. The *t*-test was used for numeric variables and Fisher test for categorical variables. The Kruskal-Wallis test for independent samples was applied to elucidate the differences in BDI scores according to gender, years of education, employment, civil status, seizure type, epilepsy syndrome, seizure control, and number of AEDs. We used simple linear correlations to evaluate the relationship between BDI scores and age, epilepsy onset, duration of epilepsy and seizure frequency. The level of statistical significance was set at $p<0.05$. We did not perform corrections for multiple comparisons because all comparisons were planned *a priori* or were complementary [25].

RESULTS

As it is shown in Table 1, when we compared the socio-demographic and seizure-related variables in both groups, we did not find significant difference in age ($p=0.422$), gender ($p=0.750$), education ($p=0.653$), employment ($p=0.694$), civil status ($p=0.519$), epilepsy duration ($p=0.166$), seizure type ($p=0.373$), epilepsy syndrome (p=0.432), number of AEDs ($p=0.102$), and suicide ideation ($p=0.309$).

Table 1. Demographic and clinical characteristics of the PWE enrolled in this study.

Variable	Pre-operatory group (n=346) (Mean±SD) / (%)	Pos-operatory group (n=122) (Mean±SD) / (%)	*p*-value
Age (years)	17-78 (40.25±12.03)	18-60 (39.26±10.69)	0.422
Epilepsy onset (years)	0-63 (12.38±10.39)	0-41 (9.5±8.1)	0.006
Duration of epilepsy (years)	2-66 (27.48±13.44)	5-56 (29.4±12.0)	0.166
Seizure frequency/month	0-30 (5.3±8.1)	0-30 (2.4±6.8)	0.001
Total BDI score	0-50 (10.14±9.8)	0-53 (7.3±9.2)	0.007
Cognitive-Affective BDI	0-38 (6.58±7.2)	0-37 (4.77±6.4)	0.016
Somatic-Performance BDI	0-30 (7.12±6.5)	0-32 (5.0±6.1)	0.002
Gender – Female – Male	198 (57%) 148 (43%)	72 (59%) 50 (41%)	0.750
Years of education	4 years (55%) 9 years (30%) 12 years (9%) M.D. (6%)	4 years (52%) 9 years (34%) 12 years (11%) M.D. (3%)	0.653
Employment	Unemployed (44%) Employed (39%) Retired (11%) M.D. (6%)	Unemployed (42%) Employed (44%) Retired (11%) M.D. (3%)	0.694
Civil Status	Single (47%) Married (45%) M.D (8%)	Single (54%) Married (43%) M.D (3%)	0.519
Seizure type	Partial (17%) Partial with generalization (39%) Unknown etiology (44%)	Partial (31%) Partial with generalization (57%) M.D. (12%)	0.373
Epilepsy syndrome	Temporal (45%) Extra-temporal (6%) Unknown etiology (49%)	Temporal (79%) Extra-temporal (7%) M.D. (14%)	0.432
Seizure control	Yes (26%) No (74%)	Yes (71%) No (29%)	<0.001
Number of AEDs	Polytherapy (66%) Monotherapy (27%) M.D. (7%)	Polytherapy (70%) Monotherapy (18%) M.D. (12%)	0.102
Symptoms of depression	No (69%) Yes (32%)	No (79%) Yes (21%)	0.028
Suicidal ideation	No (88%) Yes (12%)	No (81%) Yes (19%)	0.309

M.D. = missing data.

The variables that were significantly different between the groups were the BDI score (p=0.007), epilepsy onset (p=0.006) and seizures frequency and control (p=0.001). The pos-operatory group had fewer symptoms of depression, earlier epilepsy onset and less seizures.

Although not significant, the pos-operatory group had more suicide ideation (19%) than the PWE in the pre-operatory group (12%). Suicide ideation was highly associated to depression before and after epilepsy surgery (p<0.001 for both groups). Before surgery 43% of PWE with symptoms of depression also had suicide ideation. After surgery this association occurred in 42% of PWE.

Thirty-two percent (n=110) of the PWE in the pre-operatory group and 21% (n=26) of PWE in the pos-operatory group had scores ≥12 on the BDI, suggesting that they had depression.

Twenty-one percent (n=23) of PWE and depression in the pre-operatory group and 69% (n=18) in the pos-operatory group were taken anti-depressants. In both groups there was an association between the use of anti-depressant and BDI scores (p=0.004 in the pre-operatory group and p=0.011 in the pos-operatory group). PWE who were taking anti-depressants had higher scores in the BDI.

The mean BDI score from the pre-operatory group was 10.13 (SD=9.79). There was no significant difference between the two subscales (p=0.686): Affective subscale (M=6.57±7.25), Somatic subscale (M=7.12±6.56). The mean BDI score from the pos-operatory group was 7.36 (SD=9.18). There was also no significant difference between the two subscales (p=0.777): Affective subscale (M=4.77±6.37), Somatic subscale (M=5.0±6.08).

BDI score, suicidal ideation and socio-demographic factors

The BDI score of the pre-operatory group was not correlated to the patients' age (p=0.253), education level (p=0.434), and marital status (p=0.658). It was associated gender (p=0.013) and employment (p=0.012). Women had significant higher scores in the BDI than men in the total BDI score (p=0.013) and the Affective BDI subscale (p=0.006), but not in the Somatic subscale (p=0.182). Unemployed patients had higher scores in the total BDI (p=0.012) in both subscales; Affective (p=0.008) and Somatic (p=0.04).

The BDI score of the pos-operatory group was not correlated to any of the socio-demographic variables, as follows: age (p=0.582), gender (p=0.751), education level (p=0.210), employment (p=0.245) and civil status (p=0.392).

The suicidal ideation (evaluated by the item 9 from the BDI) was not associated to any of the socio-demographic variables in both groups as follows (pre-operatory group p-value/pos-operatory group p-value): age (p=0.622/p=0.856), gender (p=0.143/p=0.273), education level (p=0.127/p=0.289), employment (p=0.5/0.092), and civil status (p=0.541/p=1.0).

BDI score, suicidal ideation and seizure-related factors

The BDI score of the pre-operatory group was not correlated to epilepsy onset (p=0.987), epilepsy duration (p=0.196), seizures type (p=0.213), epilepsy syndrome (p=0.408), and number of AEDs (p=0.149). Seizures frequency was correlated to BDI total score (p=0.002) and both subscales; Affective subscale (p=0.008) and Somatic subscale (p=0.002). Seizures control for six months or more was correlated to BDI total score (p<0.001) in both subscales; Affective subscale (p<0.001) and Somatic subscale (p<0.001).

The BDI score of the pos-operatory group was not correlated to epilepsy onset (p=0.169), epilepsy duration (p=0.754), seizures frequency (p=0.315), seizures type (p=0.283), epilepsy syndrome (p=0.673), and number of AEDs (p=0.462). The only seizure-related variable that was correlated to BDI total score and both subscales was the control of seizures for over six months (p=0.001).

When we associated the suicidal ideation in both groups (p-value pre-operatory/p-value pos-operatory) we did not find significant difference in the following variables: epilepsy onset (p=0.736/p=0.845), epilepsy duration (p=0.345/p=0.850), epilepsy syndrome (p=0.535/p=0.304), seizures type (p=0.842/p=0.214), and number of AEDs (p=1.0/p=0.728). The suicidal ideation was associated to the seizures frequency (p=0.024/p=0.006) and control (p=0.012/p=0.011) before and after epilepsy surgery.

DISCUSSION

The present study investigated the association of socio-demographic and seizure-related variables with symptoms of depression in PWE. Our results confirm the view that depression is frequently associated to epilepsy (32% in the pre-operatory group and 21% in the pos-operatory group). It additionally showed that before epilepsy surgery female gender, unemployment and high seizure frequency are associated factors for the occurrence of depression symptoms. After epilepsy surgery, the only factor associated high level of depression symptoms was the lack of seizure remission. Suicidal ideation was associated to seizures frequency and seizure control before and after epilepsy surgery.

We evaluated the symptoms of depression in PWE using the evaluation of BDI total score and its Affective and Somatic subscales. While the Affective aspect is associated to the "mental aspect" of depression, the Somatic aspect is associated with disease severity. Our findings suggest

that controlling for disease severity, the Somatic Aspect may improve. Our study did not show any difference in the BDI subscales when comparing them to any of the socio-demographic and seizure-related variables, except for the female gender. Women with epilepsy appeared to have more severe symptoms of depression in the BDI total score and in the Affective aspect, but not in the Somatic aspect, but this association occurred only in the group with more frequent seizures (pre-operatory group), and not in the pos-operatory group which had better seizure control.

The prevalence of female gender in depression has extensively been reported, with odds ratios in major epidemiological surveys falling between 1.6:1 and 3.2:1.[26,27] This preponderance seems to emerge in early adolescence and continues through adulthood.[28,29] However, there is no particular definite elucidation to explain why depression is more common in women.[30-32] Besides the previous knowledge of higher prevalence of depression in women, the effect of gender on depression in PWE has been highly controversial, most likely due to different methodological approaches. Some studies concluded that men are overrepresented in depressed PWE.[33-35] Others reported opposite results with gender having either no effect[36] or with a preponderance of female PWE and depression.[37] Our results agree with this latter study, showing a significant association between female gender and depression in epilepsy.

Many studies have shown that PWE are twice as likely as people without epilepsy to be unemployed.[38,39] The unemployment rate of PWE is two to four times greater than that of the general population.[38]

Employment, despite its economic value, indicates social acceptance and leads to sense of worth. Many previous studies have reported a relationship between unemployment and ill health,[40] poor quality of life[41,40] and depression.[40,42,43]

Our study found a relationship between unemployment in PWE and symptoms of depression. Unemployment may be a predictor for depression in epilepsy or the other way around. Considering the high prevalence of epilepsy and depression, this situation creates a huge social problem. One study[44] indicated many reasons for job loss in epilepsy, such as depressed mood, general lack of activity, cognitive disturbances, physical disabilities, poor self-esteem, social isolation, employer discrimination, stigmatization, fear of having a seizure in the workplace, pessimistic attributional style and changes in biological rhythms that negatively influence their ability to work. Because PWE frequently are socially isolated and epilepsy is still professed as some sort of mental disease, patients have serious problems in continuing education or maintaining employment.[45] It is uncertain whether such phenomena are separate from or secondary to depression. This may be a bidirectional effect: depression may lead to low income and unemployment, and unemployment may lead to depression[46]

In addition, uncontrolled seizures may be a risk factor for depression and suicide behavior.[47] Seizure control has consistently been found to be a predictor of depression[48,49] as indicated by our findings. High seizure frequency was the only aspect that was related to suicide ideation before and after epilepsy surgery. It makes the frequency an important predictor for depression and suicide, what calls attention for appropriate treatments and the routine of screening for depression in patients with refractory epilepsy.

Although before surgery the female gender and unemployment were associated to more severe symptoms of depression together with the high seizures frequency and seizures control, after epilepsy seizure when the greater expectative was to have fewer seizures, the seizures control was the only factor that was associated to symptoms of depression. As already observed in our previous studies (Barioni Salgado et al., 2008), it seems that after surgery patients expectations to be free of seizures is so high that failure of postoperative seizure control disrupts all their plans of future and leads to depression and suicide ideation.

Neurologists do not routinely screen PWE for depression,[50] Consequently, depression is under recognized and untreated in PWE,[13] In our study 32% of the pre-operatory group and 21% of the pos-operatory group had symptoms of depression. From this group only 32% of the pre-operatory group and 69% of the pos-operatory group was taking antidepressants. In the same line of previous studies,[51,52] our data showed that PWE using antidepressants were significantly more likely to have more symptoms of depression. It may be due to the fact that the ones who were receiving antidepressants were the ones with the most severe depression, but treatment was either ineffective or they were too early in treatment that could not show its benefit.

One limitation of our study was that being retrospective. Another limitation is the fact that we could not take into account the onset of depression, the recurrence of depression symptoms and other variables associated with depression and/or suicidal thoughts, such as, recent lost of an important person, past history of depression, family history of depression, physical and/or sexual abuse. Our findings add to the understanding of depression in PWE and highlight the need to investigate this further with prospective studies.

In conclusion, our results confirm the general view that depression is common in PWE and provide further insight to the association of depression with high seizure frequency and other socio-demographic factors.

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Review Article

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Autismo e Epilepsia: Modelos e Mecanismos

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RESUMO

O autismo está associado a epilepsia em aproximadamente 30% dos casos com evidências sugerindo a mesma neurofisiopatologia. O mecanismo comum em ambas doenças ainda não está bem definido e a heterogeneidade dos sintomas clínicos nas crianças com transtorno do espectro autista e epilepsia reforça a importância de uma abordagem que inclui a investigação de etiologias biológicas através de estudos de neuroimagem, dos processos inflamatórios, de genética e neuroquímica. Aqui, iremos revisar os principais aspectos da associação entre autismo e epilepsia.

Unitermos: autismo, epilepsia, neurobiologia, neuroinflamação.

ABSTRACT

Autism and epilepsy: models and mechanisms

Autism is associated with epilepsy in early childhood in almost 30% of children with either disorder, with evidence suggesting the same neurophysiopathology. The common mechanism in both diseases is not well defined and the heterogeneity of clinical symptoms in children with autism spectrum disorder (ASD) and epilepsy highlights the importance of a comprehensive assessment that includes investigation of underlying biological etiologies through neuroimaging, inflammatory, genetic and neurochemistry studies. Here, we review the main aspects of this association between autism and epilepsy.

Keywords: autism, epilepsy, neurobiology, neuroinflammation.

INTRODUÇÃO

O autismo é um transtorno do desenvolvimento caracterizado por prejuízos na comunicação verbal e não verbal, déficits qualitativos de interação social e repertório restrito de atividades e interesses, presentes antes dos 3 anos de idade.[1] Na próxima edição do Manual Diagnóstico e Estatístico da Associação Americana de Psiquiatria (DSM-5) que será publicada em 2013, o autismo será representado por apenas uma única categoria: os Transtornos do Espectro Autista (TEA). Nesta nova classificação, os déficits de interação social e de comunicação pertencerão a um único critério. Isto porque os déficits de comunicação e interação social sociais são inseparáveis e mais precisamente considerados como um único conjunto de sintomas. O segundo critério consiste em interesses restritos e repetitivos exibidos por pelo menos dois dos seguintes: comportamentos motores ou verbais estereotipados, ou comportamentos sensoriais incomuns; e aderência excessiva às rotinas e padrões de comportamento ritualizados e restritos.[2]

Na ausência de um marcador biológico o diagnóstico permanece clínico e a suspeita diagnóstica precoce possibilita uma adequada intervenção.[3]

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A prevalência vem aumentando nas últimas décadas e dados recentes estimam que 1 em cada 88 crianças apresentem o transtorno do espectro autista,[4] que além das caracteristicas acima mencionadas pode vir acompanhado por resposta alterada a estímulos sensoriais, agressividade, déficits cognitivos, atraso do desenvolvimento motor e especialmente epilepsia.

Este espectro de apresentações sugere uma heterogeneidade neurobiológica e várias teorias surgiram na tentativa de esclarecer os fatores de risco e mecanismos associados. Apesar de diversas alterações terem sido associadas ao autismo, anormalidades inflamatórias, neuroquímicas e de hipoperfusão neural parecem ser as mais consistentes.[5,6]

É interessante observar que desde a primeira descrição de Kanner, em 1943, a associação entre transtorno do espectro autista e epilepsia já havia sido descrita.[7]

Aproximadamente 30% das crianças com autismo desenvolvem crises epilépticas ou alterações eletroencefalográficas sem, no entanto, apresentar patologia de base específica, permanecendo indefinido se as crises epilépticas ou as alterações encontradas são causa ou comorbidade.[8]

O autismo e a epilepsia podem ocorrer juntos por razões diferentes. Há crianças que podem apresentar epilepsia e autismo por terem herdado ambas as condições; outras podem ter desenvolvido a epilepsia como conseqüência de uma patologia cerebral comum, como a rubéola congênita ou a síndrome do X-Frágil; e há aquelas que em que o autismo seria decorrente de um processo epiléptico que interfere no funcionamento de redes específicas atreladas a comunicação e ao comportamento social, como por exemplo, o sistema límbico.[9]

Estudos sugerem uma distribuição bimodal quanto ao risco de epilepsia, com o primeiro pico ocorrendo no primeiro ano de vida e o segundo após os 10 anos.[10] A epilepsia pode ter início antes do desenvolvimento da linguagem ou a linguagem pode sofrer regressão após o início das crises epilépticas como ocorre na Síndrome de Landau Kleffner, por exemplo.[11,12]

A questão é quais são os indícios que nos fazem acreditar que crises epilépticas recorrentes ou uma atividade elétrica anormal sejam responsáveis por alterações cognitivas, comportamentais ou de linguagem e qual o mecanismo em comum envolvido nestas duas patologias.

NEUROBIOLOGIA DO AUTISMO

Apesar da evidência epidemiológica de que uma disfunção cerebral esteja presente no autismo os primeiros estudos de neuroimagem não foram capazes de reproduzir esta suspeita de forma localizada ou consistente. Investigações mais recentes, incluindo ressonância magnética com volumetria, demostraram alterações principalmente no que se refere a volume cerebral sugerindo que determinadas áreas, como giro cingulado, caudado, cerebelo, giro fusiforme, giro frontal superior e inferior, giro temporal superior, tálamo, ínsula e cortex occipital apresentam aumento de substância cinzenta e redução de substância branca o que pode explicar o prejuízo da conectividade entre as diferentes regiões.[13,14]

A novidade surgiu com o advento de técnicas funcionais como tomografia com emissão de pósitron (PET), SPECT e ressonância magnética funcional que têm permitido estudar as disfunções corticais presentes nas crianças com autismo.[15]

Em 1995, Zilbovicius e colaboradores relataram uma hipoperfusão frontal transitória nas crianças com autismo entre 2 e 4 anos de idade sugerindo um amadurecimento metabólico tardio nestas crianças quando comparadas a crianças mais velhas. Mais recentemente, outros grupos, através de estudos de PET ou SPECT, identificaram hipoperfusão da região temporal, incluindo giro temporal superior e sulco temporal superior. Estes achados sugerem uma conexão entre disfunção do lobo temporal, autismo e patologias do lobo temporal, como epilepsia,[6,16,17] com desorganização das redes corticais.[15] Isso foi observado, por exemplo, nas crianças com Síndrome de West e espasmos infantis no qual o hipometabolismo temporal bilateral precoce está fortemente relacionado ao posterior surgimento de sintomas de autismo, bem como nas crianças com esclerose tuberosa em que há uma íntima relação entre tuberos localizados no lobo temporal, crises epilépticas e transtorno autista.[18-20]

A gravidade, impacto e a variedade de sintomas associados ao autismo ou a determinadas síndromes epilépticas refletem anormalidades tanto estruturais quanto funcionais bem como disfunções focais ou globais da rede neuronal.[12]

AUTISMO, EPILEPSIA E NEUROINFLAMAÇÃO

Durante décadas acreditou-se que não havia processo inflamatório no autismo já que não se identificavam evidências de inflamação ou gliose e as imagens de ressonância eram normais. Mais recentemente, porém, Vargas e colaboradores através de técnicas de imunohistoquímica e ELISA conseguiram demonstrar neuroinflamação no cérebro e líquido céfalo-raquidiano de indivíduos com autismo.[21,22] O processo inflamatório que ocorre no cérebro destes pacientes parece refletir o envolvimento inato do sistema nervoso central mas não do sistema imune adaptativo, uma vez que inclui ativação de microglia e astroglia mas não de linfócitos, enquanto o perfil de citocinas apresenta elevação as custas de proteina quimioatraente a macrófagos-1(MCP-1) e fator de crescimento tumoral-β1. Os achados indicam que as reações neuroimunes desempenham um papel patogênico

em uma proporção de pacientes com autismo, e é provável que as anormalidades metabólicas de inflamação e estresse oxidativo estejam relacionadas às alterações de estrutura e função encontradas nestes pacientes.[21,23] Uma outra possibilidade é que a neuroinflamação e o estresse oxidativo associado possam levar a excitoxicidade causando ativação cortical e aumento da atividade neuronal.[21]

Em 2009, Li e colaboradores também determinaram a atividade imunólogica do cérebro de autistas e os resultados foram semelhantes ao de Vargas com aumento das citocinas pro-inflamatórias (fator de crescimento tumoral α, IL-6 e GM-CSF) no cérebro de pacientes com transtorno do espectro autista. O papel do fator de crescimento tumoral α como agente neuromodulatório tem sido descrito no processo de desenvolvimento cerebral e pode estar envolvido na modulação da transmissão glutaminérgica. O excesso de TNF-α provoca efeitos excitotóxicos nos receptores NMDA, levando à ativação microglial e estas alterações são as mesmas encontradas em modelos de inflamação indutores de atividade epiléptica.[24,25]

A ROTA METABÓLICA NO AUTISMO E EPILEPSIA

Vários defeitos metabólicos têm sido associados a sintomas autistas e epilepsia, com uma prevalência mais elevada do que a encontrada na população geral e incluem: fenilcetonúria, deficiência de adenilsuccinase, deficiência de creatina, deficiência de biotinidase e forma infantil de lipofucsinose ceróide, principalmente.[26]

Fenilcetonúria

É um dos transtornos mais prevalentes do metabolismo dos aminoácidos e a possibilidade diagnóstica precoce através de testes de triagem neonatal permitiu tratamento preventivo através de dieta.[27] Nas crianças sem tratamento, a hiperfenilalanina pode causar redução de mielina, perda neuronal e redução das conexões interneuronais e de densidade de neurotransmissores levando ao surgimento de crises epilépticas e sintomas de autismo clássico.[28]

Deficiência de creatina

A deficiência de creatina é uma desordem rara, descrita pela primeira vez em 1994.[29]

Duas enzimas são necessárias para a síntese de creatina: arginina glicina amidinotransferase (AGAT) e guanidinoacetato metiltransferase (GAMT).[30]

A creatina atua de maneira diferenciada no Sistema Nervoso Central e está envolvida na atividade da Na^+/K^+ ATPase, na liberação de neurotransmissores, na homeostase de Ca^{++} e na manutenção dos potenciais de membrana além de sua função no processo de alongamento dendrítico e axonal.[31,32]

As síndromes de deficiência de creatina podem ser consequência de distúrbio da síntese da creatina (AGAT ou GAMT) ou por defeito na proteína transportadora (SLC6A8) e a deficiência pode ser demonstrada por ressonância magnética de encéfalo com espectroscopia.[33]

A deficiência de GAMT inclui um fenótipo mais complexo onde aparecem os quadros de epilepsia refratária e sintomas autistas, provavelmente secundários a ação tóxica do acúmulo de guanidinoacetato que age sobre os receptores GABA.[32,34,35]

Deficiência de adenilsuccinase

Aproximadamente metade dos pacientes apresenta características autísticas como incapacidade para manter contato visual, comportamento repetitivo e estereotipado, agitação e autoagressão. O eletroencefalograma pode ser normal no início com surgimento posterior de alterações e crises epilépticas. Estudos experimentais demonstraram que a infusão de succinilaminoimidazol carboxamida ribosídeo provoca dano neuronal em regiões específicas do hipocampo causando deformidade. A alteração na forma do hipocampo em crianças com transtorno do espectro autista é similar ao padrão encontrado em paciente com epilepsia de lobo temporal mesial.[36]

O PAPEL DOS NEUROTRANSMISSORES

Serotonina

As anormalidades serotoninérgicas estão presentes tanto no autismo quanto na epilepsia e esta associação pode fornecer mais uma pista para os mecanismos que se sobrepõem nas duas condições. A serotonina desempenha um importante papel neurotrófico durante o desenvolvimento cerebral precoce e evidências sugerem que as alterações no metabolismo ou transporte de serotonina (ou triptofano) no período pré natal e durante o desenvolvimento pós natal precoce possam levar a modificações na conectividade talamocortical e intracortical a qual resulta em uma predisposição à epilepsia e autismo.[37-42]

Dopamina

A dopamina é uma catecolamina sintetizada a partir da tirosina. O interesse no papel da dopamina, no autismo, surgiu com a observação que alguns bloqueadores dopaminérgico (antipsicóticos) são eficazes no tratamento de certos aspectos do transtorno, como hiperatividade, estereotipias e auto agressão e os estudos em animais confirmaram que as estereotipias e hiperatividade podem ser induzidas a partir de uma aumento no funcionamento dopaminérgico.[43]

Recentemente tem havido um maior interesse pelo papel da dopamina também na patofisiologia das epilepsias com vários relatos de alterações na neurotransmissão

dopaminérgica em modelos animais de epilepsia principalmente àquelas relacionadas a densidade de receptores da dopamina no hipocampo.[44] Enquanto se acredita que o desequilíbrio no sistema glutamato-GABA (ácido gamaaminobutírico) seja a base da epilepsia, a dopamina influenciaria a expressão das crises.[45,46] Apesar disso, o impacto da dopamina no início das crises, progressão da doença e sobre o desenvolvimento ainda é pouco compreendido e alguns estudos sugerem que as alterações no sistema dopaminérgico, encontradas em pacientes com epilepsia, seriam o resultado da atividade epiléptica recorrente e poderiam explicar a fisiopatologia das epilepsias e suas comorbidades (autismo, ansiedade e depressão).[47,48]

CONCLUSÃO

A frequência de epilepsia em crianças com autismo é elevada bem como é comum observarmos regressão autística em síndrome epilépticas mesmo na ausência de crises clínicas.

A convergência de achados e modelos sugere uma sobreposição significativa entre autismo e epilepsia. A diversidade de apresentações das duas síndromes dificulta a identificação de um único mecanismo e é provável que a combinação de diferentes fatores esteja envolvida.

Esta breve revisão destacou os principais achados da última década na tentativa de explicar a íntima associação entre autismo e epilepsia. O desafio em identificar o mecanismo causa-efeito persiste e pequisas futuras devem ser direcionadas para esta questão.

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