

Revista Mexicana de Neurociencia



Academia
Mexicana de
Neurología, A.C.

Publicación oficial de la Academia Mexicana de Neurología A.C.

VOLUME 23 - NUMBER 5 / September-October 2022 – ISSN: 2604-6180

www.revmexneurociencia.com

Editorial

Editorial

Antonio Arauz and Luis Dávila-Maldonado

163

Neurodevelopmental and neurodegeneration

Sergio Iván Valdés Ferrer

164

Original articles

Alterations in neurodevelopment in children under 5 years of age in two states of the Mexican Republic

Josefina Ricardo-Garcell, Francia Guadarrama-Celaya, Gloria A. Otero-Ojeda, René F. Rodríguez-Valdés, Liane Aguilar-Fabré, Hebert L. Hernández-Vázquez, Pablo García-Solís, Juan C. Solís-S, Carlota García, Javier Ávila-Morales, and Hebert L. Hernández-Montiel

165

Opinion and prevalence of use of central nervous system stimulants in open population: results of an electronic survey

Paulina Flores-Medina and Paul Carrillo-Mora

171

Review articles

The influence of gut brain axis in neurodegenerative diseases: short review

Renata Murguiondo-Pérez, Óscar Vidal Alcántar-Garibay, Efraín Weintraub Ben-ZiÓN, Enrique Blancarte-Hernández, Emilio Tejerina-Marion, Ericka Cristina Loza-López, Mario Galindo-Ruiz, and Germán Rivera-Monroy

177

Aspects of neurodevelopment between autism spectrum disorders and epilepsy

Paola Núñez-Contreras, Daniela Granado-Rocha, Maritza Carvajal-Game, and Ana M. Torres-Perez

183



PERMANYER
www.permanyer.com

Editorial

Antonio Arauz

Editor-in-chief

Dear colleagues, friends, and readers:

We are proud to announce that Revista Mexicana de Neurociencia has been included in the Emerging Sources Citation Index™, by Clarivate 2022.

This is the result of the constant work of our committee, editors, reviewers, and authors, whose efforts have placed our journal in a framework of highly regarded academic and scientific literature.

This is only the beginning, as a great challenge still lays ahead of us. Now more than ever, we must strive for excellence and continue harvesting the fruits of our

labor. **Revista Mexicana de Neurociencia** can only grow further in the coming years to achieve the ultimate goal: the Impact Factor. But most importantly, we should aim to keep the trust of our readers, issue by issue, and article by article.

Once again, we would like to thank you for your collaboration and we hope that this news will bring a smile to your face, as it did ours.

Here's to the future!

Board of Directors and Editorial Committee
Revista Mexicana de Neurociencia

***Correspondence:**

Antonio Arauz-Góngora,

E-mail: antonio.arauz@prodigy.net.mx

2604-6180 / © 2022 Academia Mexicana de Neurología A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 08-07-2022

Date of acceptance: 08-07-2022

DOI: 10.24875/RMN.M22000091

Disponible en internet: 19-10-2022

Rev Mex Neuroci. 2022;23(5):163

www.revexneurociencia.com

Neurodevelopmental and neurodegeneration

Sergio Iván Valdés Ferrer*

Department of Neurology and Psychiatry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Neurodevelopmental issues in lower- and middle-income countries are incompletely understood. The current issue of *Revista Mexicana de Neurociencia* has two timely articles on neurodevelopment: the first one by Ricardo-Garcell and colleagues evaluated neurodevelopmental milestones in children during the first 5 years in urban, suburban, and rural communities in Queretaro and Toluca, two large cities in Mexico. For that, these authors relied on a validated electronic tool. Reassuringly, their results are not different from those observed elsewhere. However, there was vast between city differences. While the study was not designed to evaluate potential causes, these results prompt further studies also aimed at evaluating causes of neurodevelopmental delays in children in Mexico. A second manuscript by Núñez-Contreras thoroughly reviews critical neurobiological aspects of autism and epilepsy,

narrowing down common mechanisms between both conditions. This review covers basic, translational, and clinical aspects.

The gut-brain axis, a two-way highway of information has gained track in the past two decades, particularly after the group of Kevin J. Tracey discovered the so-called cholinergic anti-inflammatory pathway, effectively launching a new field of reflex neuroimmune communication. In this issue, Murguiondo-Pérez and colleagues succinctly review key aspects of the gut-brain axis from the perspective of neurodegenerative disease.

We hope that this issue will be of interest to our readers, particularly those interested in neurodevelopment and neurodegeneration.

Sergio Iván Valdés Ferrer
Co-Editor, Revista Mexicana de Neurociencia

Correspondence:

*Sergio Iván Valdés Ferrer

E-mail: sergio.valdesf@incmnsz.mx

2604-6180 / © 2022 Academia Mexicana de Neurología A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 05-09-2022

Date of acceptance: 19-09-2022

DOI: 10.24875/RMN.M22000091

Available online: 19-10-2022

Rev Mex Neuroci. 2022;23(5):164

www.revmedneurociencia.com

Alterations in neurodevelopment in children under 5 years of age in two states of the Mexican Republic

Josefina Ricardo-Garcell^{1†}, Francia Guadarrama-Celaya², Gloria A. Otero-Ojeda², René F. Rodríguez-Valdés³, Liane Aguilar-Fabré³, Hebert L. Hernández-Vázquez⁴, Pablo García-Solís⁵, Juan C. Solís-S⁵, Carlota García⁵, Javier Ávila-Morales⁶, and Hebert L. Hernández-Montiel^{3*}

¹Neurodevelopment Unit Dr. Augusto Fernández Guardiola, Neurobiology Institute, UNAM, Juriquilla, Querétaro; ²Faculty of Behavioral Science, Universidad Autónoma del Estado de México, Toluca, State of Mexico; ³Neurodiagnosis and Rehabilitation Unit Dr. Moisés López González, Neurobiology and Cellular Bioengineering Laboratory, Faculty of Natural Sciences, Universidad Autónoma de Querétaro, Juriquilla, Querétaro; ⁴Faculty of Medicine, Universidad Autónoma de Querétaro, Santiago de Querétaro, Querétaro; ⁵Department of Biomedic Research, Faculty of Medicine, Universidad Autónoma de Querétaro, Santiago de Querétaro, Querétaro; ⁶University Health System, Faculty of Medicine, Universidad Autónoma de Querétaro, Santiago de Querétaro, Querétaro. Mexico

Abstract

There are more than 1 billion people with disabilities worldwide, with 16% of children having some type of neurodevelopmental disorder (ND). In Mexico, 6% of the population presented some disability; however, there is a lack of data on ND in children under 5 years of age. **Objective:** The objective of this study was to determine the prevalence of neurodevelopmental alterations in children under 5 years of age in urban, suburban, and rural populations from two states of Mexico. **Methods:** This was an observational and cross-sectional design study. We included 501 clinically healthy children from 0 to 60 months of age, from urban, suburban, and rural populations from the state of Querétaro (201) and from the State of Mexico (300). Neurodevelopmental alterations were detected through the electronic N-PED system, exploring areas of neurological development of language, psychomotor, and sensory (auditory and visual). The positive subjects were clinically assessed to confirm the diagnosis. **Results:** A 14.7% prevalence of ND was found, with a significant difference between Querétaro (8.9%) and the State of Mexico (18.7%). Language alterations were significantly different for both states (4.9% and 16% for Querétaro and the State of Mexico, respectively). **Conclusions:** The prevalence of ND and language alterations presented significant differences between the two evaluated states.

Keywords: Neurodevelopmental deviations. Language. Psychomotor. Sensory.

Alteraciones del neurodesarrollo en niños menores de 5 años en dos estados de la República Mexicana

Resumen

Hay más de mil millones de personas con discapacidad en todo el mundo, el 16% de los niños tiene algún tipo de trastorno del desarrollo neurológico (DN). En México, 6% de la población presenta alguna discapacidad; sin embargo, faltan datos en niños menores de 5 años. **Objetivo:** Determinar la prevalencia de alteraciones del neurodesarrollo en menores de 5 años, en poblaciones urbanas, suburbanas y rurales, de 2 estados de México. **Métodos:** Estudio observacional, de diseño

Correspondence:

*Hebert L. Hernández-Montiel
E-mail: hebert@uaq.mx

Date of reception: 03-11-2021

Date of acceptance: 20-12-2021

DOI: 10.24875/RMN.21000075

Available online: 19-10-2022

Rev Mex Neuroci. 2022;23(5):165-170

www.revexneurociencia.com

2604-6180 / © 2021 Academia Mexicana de Neurología A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

transversal. Se incluyeron 501 niños, clínicamente sanos, de 0 a 60 meses de edad, de poblaciones urbanas, suburbanas y rurales de Querétaro (201) y del Estado de México (300). Se detectaron alteraciones del neurodesarrollo a través del sistema electrónico N-PED, explorando áreas del lenguaje, psicomotor y sensorial (auditivo y visual). Los sujetos positivos fueron evaluados clínicamente para confirmar el diagnóstico. Resultados: Se encontró una prevalencia de trastornos del DN de 14.7%, con una diferencia significativa entre Querétaro (8.9%) y el Estado de México (18.7%). Las alteraciones del lenguaje fueron significativamente diferentes para ambos estados (4.9% y 16% para Querétaro y el Estado de México, respectivamente). Conclusiones: La prevalencia de trastornos del DN y del lenguaje, presentaron diferencias significativas entre los dos estados evaluados.

Palabras clave: Desviaciones del neurodesarrollo. Lenguaje. Psicomotor. Sensorial.

Introduction

According to the WHO and the World Bank, it is estimated that more than one billion people live with a disability in the world¹. Of these, alterations in psychomotor neurodevelopment could constitute up to 16%²; these appear as alterations in gross and fine motor coordination, language, speech, consciousness, social interaction, and activities of daily life. Its etiology is linked to psychomotor retardation and age and is manifested by specific alterations in adaptation and learning skills^{3,4}. The early identification of these alterations allows the application of rehabilitation therapies that improve the limitations⁵.

This present study made a comparison of the prevalence of neurodevelopmental disorders (ND) found in urban, suburban, and rural populations of the States of Querétaro and Mexico, using the N-PED system. This electronic screening device allows the detection of alterations in the psychomotor development of children under 5 years of age⁶. The equipment is portable, automated, and validated for the early detection of neurodevelopmental alterations. It evaluates areas of language, psychomotor, and sensory (visual and auditory). The lack of accreditation in any of the items, selected automatically by the software according to the age group, in any of the variables, results in the overall non-accreditation of the test. Each unapproved subject required a specialized clinical evaluation for their definitive diagnosis^{7,8}. The NPED degrees of confidence and reproducibility were previously validated.

Materials and Methods

The study design was observational and cross-sectional. This research project was carried out in two states of the Republic, Querétaro and the State of Mexico. In the first, a total of 201 children were studied, 67 children from an Urban community (Q1), 67 from a Suburban community (Q2), and 67 more from a Rural community

(Q3). In the second state, a total of 300 children were studied: 100 children from one Urban community (T1) and 200 children from two suburban communities (T2 and T3, 100 children each). All the children studied were between 0 and 60 months of age and in all cases, the studies were carried out in the presence of at least one parent. The N-PED system was applied before individual training and qualification by the specialists who developed the computerized instrument. The consistency of the evaluators' results was verified through an inter-trial evaluation that is not included in this work. For the application of the instrument, an informative talk was previously held with the parents of each of the children and in all cases, only those children where the parents agreed were accepted for their participation, after signing a letter of confirmation informed consent. The project was also approved by a Bioethics committee in each case, and scientific research should be conducted in accordance with the World Medical Association Code of Ethics (Helsinki Declaration) for experimentation involving human beings. The evaluations were carried out in children with no known pathological history, who attended the agreed appointments for the examination with the N-PED system and who did not manifest acute diseases that prevented or altered the results of the evaluation. The children included in the study were evaluated on their usual schedule for preschool activities. The N-PED system allowed the detection of neurodevelopmental alterations in the areas of language, psychomotor, and sensory (auditory and visual). This system considers the test as "not accredited" when the performance of the evaluated child is not performed according to what is established as the normal expected for any of the items⁶. Once the evaluation was completed, the individuals who did not accredit the test were submitted to a clinical and electrophysiological assessment of the abnormalities detected, where the diagnosis was confirmed. Subsequently, a medical report was delivered and it was referred to the health services of each state for treatment. It is worth

mentioning that all the children were evaluated with the tests considered as the gold standard for the detection of language, psychomotor, and sensory disorders. Subsequently, the data obtained through the N-PED system was emptied, with the purpose of its subsequent analysis. Descriptive statistics were performed, establishing the prevalence of ND in the urban population. Subsequently, the Chi-square test and Fischer's exact test were used to determine the existence of significant statistical differences ($p < 0.05$).

Results

The analysis of the results corresponds to a global population of 501 children under 5 years of age, 201 for the State of Querétaro and 300 for the State of Mexico. In the state of Querétaro, three communities with 67 children each group were analyzed: urban (Q1), Suburban (Q2), and Rural (Q3). For the State of Mexico, three communities with 100 children each group were also included: urban (T1) and two Suburban communities (T2 and T3). The study included 105 children 0-12 months of age; 89 children from 13 to 24 months; 79 children from 25 to 36 months; 73 children from 37 to 48 months; and, finally, 155 children from 49 to 60 months of age (Table 1). Of the total sample evaluated, 85.23% of the children were classified as having normal neurodevelopmental by the neurodiagnostic test. A total of 74 children, corresponding to 14.77% of the cases, showed problems in their neurodevelopment, language alteration was the most frequent globally with 11.57%, psychomotor alterations were presented in 4.79% and sensory alterations were 3.98%, with auditory alterations in 2.59% and visual alterations in 1.39% (Table 2).

Next, an analysis of the neurodevelopmental alterations was carried out, comparing the results of the two states. For the State of Querétaro, a global failure of 8.95% was found, showing a significant difference to that found in the State of Mexico, which was 18.7%. The analysis of the prevalence of language disorders also showed a significant difference between the two states, with a prevalence of 4.97% for Querétaro and 16% for the State of Mexico. The alterations in the psychomotor area did not show significant differences, with 3.48% for Querétaro and 5.7% for the State of Mexico.

Finally, in the analysis of sensory alterations, there were no significant differences between Querétaro and Estado de México, with auditory alterations 1.49% and

3.3% and visual alterations of 1.99% and 1%, respectively (Table 3).

Subsequently, a comparison was made between the communities of both states, finding statistically significant differences in the presence of global failure between the community T3 (23%) with the communities (10.45%), Q2 (5.97%), and Q3 (10.45%). When the language failures results were analyzed, significant differences were found between the Q2 community, that did not present any cases, and the Q3 (8.95%), T1 (13%), T2 (13%), and T3 (22%) communities. A significant difference was also found in language alterations between the Q3 community (8.95%) and the T3 community (22%). The results of the evaluations in the psychomotor and visual sensory area did not show significant differences between the studied communities. Finally, the auditory sensory evaluation registered significant differences between the T1 community (8%) and the T2 (1%) and T3 (1%) communities, all from the state of Mexico (Table 4).

Discussion

The present work tries to emphasize the need for the early diagnosis of ND in children under 5 years of age, which are prevalent in populations from different socio-cultural strata. The performance of the normal healthy children examined for a second time was 88.6% compared to their first evaluation ($p < 0.0001$; Kendalls tau $b = 0.72$, $c = 0.57$); (F. Guadarrama, E. Santos, D. Aguirre, unpublished data). In a previous work, NPED was tested in a neighborhood of the City of Habana, Cuba, against the results studies of specialized clinical and neurophysiological cases, it is considered to be the gold standard, and at the time, the sensitivity and specificity of the NPED instrument were determined to be, respectively, 95% and 86%⁹.

It is estimated that approximately 16-18% of children could present some type of normal neurodevelopmental deviations due to sensory deficits (auditory or visual), delays in psychomotor development, and language and/or communication disorders¹⁰⁻¹². Early detection and intervention can lessen unfavorable consequences and may allow children to achieve optimal development of their abilities. For this reason, it is very important to identify children who may present deviations in normal neurological development, with the use of an easy-to-apply tool. National health systems in any country could benefit from early detection tools that can be applied quickly and easily, without requiring highly specialized personnel.

Table 1. Distribution of children by age and by community

Age (months)	Community Q-1	Community Q-2	Community Q-3	Community T-1	Community T-2	Community T-3	Total
0-12	12	8	9	41	19	16	105
13-24	14	19	10	15	21	10	89
25-36	14	1	7	20	25	12	79
37-48	8	3	9	8	25	20	73
49-60	19	36	32	16	10	42	155
Total	67	67	67	100	100	100	501

Q1: Queretaro urban community, Q2: Queretaro suburban community, Q3: Queretaro rural community, T1: urban community State of Mexico, T2: suburban community State of Mexico, T3: suburban community state of Mexico.

Table 2. Number of cases and percentage of failure by areas

Areas	N	%
Global failure	74	14.77
Language	58	11.57
Psychomotor	24	4.79
Vision	7	1.39
Auditory	13	2.59

The alteration in the language area was the most frequent neurodevelopmental alteration found in the study. N: number of cases, %: percentage.

Table 3. Percentage of failures by state

Areas	Q-% (201)	T% (300)	p (Chi-square)	p (Fisher)
Global failure	8.95	18.7	0.0026	0.0028
Language	4.97	16	0.0001	<0.0001
Psychomotor	3.48	5.7	0.1576	0.2046
Vision	1.99	1	0.4817	0.7045
Auditory	1.49	3.3	0.1365	0.1639

The analysis of the results showed significant differences in global failure and in the language area for both states. Q. Querétaro: 210 children. T. State of Mexico: 300 children.

State of Mexico, it was 18.7%, prevalences that are within the published ranges for these alterations^{2,13-15}. A study carried out in Turkey reported a prevalence of ND of 18.9%, using the Denver II test¹⁶.

The experience of the health team, the age of the child, the population characteristics, as well as the socioeconomic level, rurality, participation in stimulation programs, and preschool education, are factors that frequently influence this variability^{17,18}. Variability in prevalences can also be found in industrialized countries; however, similar to what occurs in developing countries, language impairments are the most prevalent impairment¹⁹. Thus, a prevalence of language disorders of around 5% has been reported in children 2-4 years of age²⁰. In the present study, a higher prevalence of alterations in language was found, followed by alterations in psychomotor development and in the sensory sphere. The need for a standardized and validated screening tool for alterations in normal psychomotor development is clear worldwide and its characteristics and performance must pass the scrutiny of the medical community^{21,22}.

The first 5 years of life constitute a period of great neuronal plasticity, in which important changes in the central nervous system and the development of sensory systems take place. As a result of this maturation process, children at birth quickly acquire skills that turn out to be crucial for their development: body movements and locomotion are perfected, language appears and evolves, as a consequence of all this, the child not only learns but also who communicates and interacts with other people. At the same time, intelligence and thinking develop^{23,24}. It has been shown that in the absence of a screening procedure, the detection of normal neurodevelopmental deviations only

The main objective of this work was to evaluate if the prevalence of ND differs between urban, suburban, and rural communities of two states of the Mexican Republic. The results obtained for the state of Querétaro confirmed a global prevalence of 8.95%, while for the

Table 4. Percentage failures by community

Areas	Community Q-1	Community Q-2	Community Q-3	Community T-1	Community T-2	Community T-3
Global failure	10.45 (7)	5.97 (4)	10.45 (7)	18 (18)	15 (15)	23 (23) (** vs. Q2; * vs. Q3)
Language	5.97 (4)	0	8.95 (6) (* vs. Q2)	13 (13)	13 (13) (** vs. Q2)	23 (23) (***) vs. Q2; * vs. Q3)
Psychomotor	4.47 (3)	2.98 (2)	2.98 (2)	8 (8)	2 (2)	7 (7)
Vision	2.98 (2)	2.98 (2)	0	1 (1)	1 (1)	1 (1)
Auditory	2.98 (2)	1.49 (1)	0	8 (8)	1 (1) (* vs. T1)	1 (1) (* vs. T1)

Data analysis showed significant differences in global failure, language and auditory sensory disturbances. The psychomotor and visual sensory area did not show significant differences. Fisher's exact test: * $p < 0.05$; ** $p < 0.01$, and *** $p < 0.001$.

happens very late in life and is therefore considerably reduced the effectiveness of any form of intervention approach²⁵.

In the present study, the results obtained after the application of the automated and computerized NPED instrument are presented in two states of the Mexican Republic, the global failure percentage of the entire sample was 14.77%. Coinciding with previous publications in similar populations²⁶⁻²⁸. Global failures found in the language were 11.57% of the cases. In a comprehensive review of the literature, Law et al. found a 12-16% prevalence of speech and language delays²⁹. Another study, conducted in Meriden, New Haven, Connecticut by Horwitz et al., estimated the prevalence of language disorders of 13.5% in children 18-23 months of age, 15% in children 24-29 months of age, and 18% in 30-39 months of age³⁰. The failures in psychomotor development reported here were 4.79%, while other authors, with a study carried out in the United Arab Emirates by applying the Denver Development Test, in a representative random sample of 694 3-year-old children, found that 8.4% had a delay in global development³¹. Furthermore, through clinical diagnostic interviews, the prevalence of clinically significant developmental disability was estimated at 2.44%. Another study, which carried out an examination of psychomotor development problems in the first level of care carried out in Argentina³², found that in 839 children, apparently healthy and under 6 years of age, who attended the healthy child clinic of three health centers, a prevalence of 15-23% of development problems for each health center. In this study, hearing failures represented 2.59% of the total sample, a level much higher than that reported by Prieve et al., from 0.1% to 0.3%; in addition, 1.39% of vision failures were found, in all cases due to refractive defects³³. A recent study,

carried out in the Dominican Republic, reported a much lower prevalence of ND, of only 2.7%³⁴.

The results obtained in this research allow us to reflect on the tools available for the detection of neurodevelopmental abnormalities at the primary level of care as well as to become aware of the important window of opportunity that we have to make an early presumptive diagnosis. The N-PED system used in our study is a valuable tool for screening and detecting ND in children under 5 years of age. This acquires greater relevance if one takes into account that in our country the lag in early detection of ND is notable; therefore, the task of analyzing our role, scope, and perspectives cannot be postponed, to contribute significantly to the reduction of preventable morbidity from this type of alterations through timely diagnosis and treatment.

Conclusions

The global prevalence of ND in children from 0 to 60 months of age from two states of Mexico was similar to that reported in similar populations both nationally and internationally. Language disorders were the area of neurodevelopmental that was most frequently affected.

Funding

Financing by Thematic Networks of Academic Collaboration, Secretary of Public Education, Mexico.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

- World Health Organization, World Bank. World Report on Disability. Geneva: World Health Organization, World Bank; 2011. Available from: http://www.who.int/disabilities/world_report/2011/en/index.html
- Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the quality standards subcommittee of the American academy of neurology and the practice committee of the child neurology society. *Neurology*. 2003;60:367-80.
- Ambalavanan N, Carlo WA, Shankaran S, Bann CM, Emrich SL, Higgins RD, et al. Predicting outcomes of neonates diagnosed with hypoxic-ischemic encephalopathy. *Pediatrics*. 2006;118:2084-93.
- Riou EM, Ghosh S, Francoeur E, Shevell MI. Global developmental delay and its relationship to cognitive skills. *Dev Med Child Neurol*. 2009;51:600-6.
- Rosenberg S, Zhang D, Robinson C, Cordellia C. Prevalence of developmental delays and participation in early Intervention services for young children. *Pediatrics*. 2008;121:E1503-9.
- Santos E, Pérez-Ábalo M, Álvarez M. Sistema de software en PDA para el pesquiasaje de desviaciones del neurodesarrollo infantil (N-PED). Certificado de depósito legal de obras protegidas. Registro CENDA. No. 2738. La Habana; 2007. Available from: <http://www.cenda.cu>
- Santos-Febles E, Gaya-Vázquez J, Pérez-Ábalo M, Flores-Contreras A, Pérez-Guerra M. NPedDesk: aplicación de escritorio para control informático de un programa de tamiz para trastornos del neurodesarrollo infantil. *Rev Mex Ing Biomed*. 2012;33:137-45.
- Santos E, Pérez-Ábalo M. N-PED Instrumento Para el Pesquiasaje de Las Desviaciones del neurodesarrollo sobre dispositivo móvil. La Habana, Cuba: Lectura presentada en el V Congreso Latinoamericano de Ingeniería Biomédica; 2011.
- Savio G, Pérez Abalo MC, Hernández D, Mijares E, Perera M. Estudio Piloto de Pesquiasaje de Trastornos Del Neurodesarrollo en Municipio Cotorro. Ciudad de La Habana, Cuba: Informe Presentado al Ministerio de Salud Pública de Cuba; 2005.
- Adhikari S, Rao KS. Neurodevelopmental outcome of term infants with perinatal asphyxia with hypoxic ischemic encephalopathy stage II. *Brain Dev*. 2017;39:107-11.
- Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. *BJOG*. 2018;125:16-25.
- Fundación INECO. Fundación INECO; 2019. Available from: <https://www.fundacionineco.org/mas-del-4-de-la-poblacion-mundial-tienetdah> [Last accessed on 2020 Dec 18].
- Birnbaum R, Michael I, Shevell D, Srouf M. Screening for developmental delay in the setting of a community pediatric clinic: a prospective assessment of parent-report questionnaires. *Pediatrics*. 2006;118:1178-86.
- Guadarrama-Celaya F, Otero-Ojeda GA, Bernardo Pliego-Rivero F, Del Rosario Porcayo-Mercado M, Ricardo-Garcell J, Cecilia Pérez-Ábalo M. Screening of neurodevelopmental delays in four communities of Mexico and Cuba. *Public Health Nurs*. 2012;29:105-15.
- Carballal-Mariño M, Gago-Ageitos A, Ares-Alvárez J, del Río-Garma M, García-Cendón C, Goicoechea-Castaño A, et al. Prevalencia de trastornos del neurodesarrollo, comportamiento y aprendizaje en Atención Primaria. *J An Pediatr*. 2018;89:153-161.
- Yılmaz D, Bayar-Muluk N, Bayoğlu B, İdil A, Anlar B. Screening 5 and 6 year-old children starting primary school for development and language. *Turk J Pediatr*. 2016;58:136-44.
- Avan BI, Raza SA, Kirkwood BR. A community-based study of early childhood sensory stimulation in home environment associated with growth and psychomotor development in Pakistan. *Int J Public Health*. 2014;59:779-88.
- Schonhaut L, Rojas P, Kaempffer A. Factores de riesgo asociados a déficit del desarrollo psicomotor en preescolares de nivel socioeconómico bajo. Comuna urbano rural, Región Metropolitana, 2003. *Rev Chil Pediatr*. 2005;76:589-98.
- Bornstein MH, Hendricks C. Screening for developmental disabilities in developing countries. *Soc Sci Med*. 2013;97:307-15.
- Wallace IF, Berkman ND, Watson LR, Coyne-Beasley T, Wood CT, Cullen K, et al. Screening for speech and language delay in children 5 years old and younger: a systematic review. *Pediatrics*. 2015;136:e448-62.
- Romo-Pardo B, Liendo-Vallejos S, Vargas-López G, Rizzoli-Córdoba A, Buenrostro-Márquez G. Pruebas de tamizaje de neurodesarrollo global para niños menores de 5 años de edad validadas en Estados Unidos y Latinoamérica: revisión sistemática y análisis comparativo. *Bol Med Hosp Infant Mex*. 2012;69:450-62.
- Sand N, Silverstein M, Glascoe FP, Gupta VB, Tonniges TP, O'Connor KG. Pediatricians' reported practices regarding developmental screening: do guidelines work? Do they help? *Pediatrics*. 2005;116:174-9.
- Hernández-Muela S, Mulas F, Mattos L. Plasticidad neuronal funcional. *Rev Neurol*. 2004;38:58-68.
- Ponton CW, Eggermont JJ, Kwong B, Don M. Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. *Clin Neurophysiol*. 2000;111:220-36.
- Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S. A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment. *Health Technol Assess*. 1997;1:1-176.
- Aguirre D, Otero G, Porcayo R, Millán L. Evaluación del cociente de inteligencia en niños en condiciones socioculturales desfavorables. *Rev Cien Ergo Sum*. 1995;2:331-4.
- Otero GA. Poverty, cultural disadvantage and brain development: a study of pre-school children in Mexico. *Electroencephalogr Clin Neurophysiol*. 1997;102:512-6.
- Otero GA, Pliego-Rivero FB, Fernández T, Ricardo J. EEG development in children with sociocultural disadvantages: a follow-up study. *Clin Neurophysiol*. 2003;114:1918-25.
- Law J, Boyle J, Harris F, Harkness A, Nye C. The feasibility of universal screening for primary speech and language delay: findings from a systematic review of the literature. *Dev Med Child Neurol*. 2000;42:190-200.
- Horwitz SM, Irwin JR, Briggs-Gowan MJ, Bosson Heenan JM, Mendoza J, Carter AS. Language delay in a community cohort of young children. *J Am Acad Child Adolesc Psychiatry*. 2003;42:932-40.
- Eapen V, Zoubeidi T, Yunis F, Gururaj AK, Sabri S, Ghubash R. Prevalence and psychosocial correlates of global developmental delay in 3-year-old children in the United Arab Emirates. *J Psychosom Res*. 2006;61:321-6.
- Lejarraga H, Menéndez AM, Menzano E, Guerra L, Biancato S, Pianelli P, et al. PRUNAPE: pesquisa de trastornos del desarrollo psicomotor en el primer nivel de atención. *Arch Argent Pediatr*. 2008;106:119-25.
- Prieve B, Dalzell L, Berg A, Bradley M, Cacao A, Campbell D, et al. New York state universal newborn hearing screening demonstration project: outpatient outcomes measures. *Ear Hearing*. 2000;21:104-17.
- Morban DA, Colomé-Hidalgo M, Torres ZL. Prevalencia de los desórdenes del desarrollo en un hospital de 3er nivel de Santo Domingo norte, República Dominicana. *Ciencia y Salud*. 2021;5:117-24.

Opinion and prevalence of use of central nervous system stimulants in open population: results of an electronic survey

Paulina Flores-Medina¹ and Paul Carrillo-Mora^{2*}

¹Faculty of Medicine, Universidad Autónoma de Sinaloa, Culiacán, Sinaloa; ²Subdivisión de Investigación en Neurociencias Clínicas, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico

Abstract

Objective: The objective of the study was to know the opinion and prevalence of use of central nervous system stimulant drugs (SDs) in healthy people in open population. **Methods:** An electronic survey was designed with 11 questions to know the frequency of use of SD, and also questions to explore previous knowledge, opinion about the risks associated with its use and about its regulation, etc. The survey was spread by electronic social networks to persons over 18 years old of any gender. Descriptive analysis and a Chi-square test were done to find associations between variables. **Results:** A total of 526 surveys were conducted, 271 male participants (51.5%) and 249 female (47.3%). The median of age was 22 years old (range 18-83 years). Median scholarship was 12 years (range 6-20 years). About 49.6% were students. About 75% had prior knowledge about stimulants, 13.6% reported prior use, 26% opined these drugs could be dangerous, and 88% opined that they should be regularized. Finally, ages between 18 and 30 years old and scholarship above high school were associated with the use of SD. **Conclusion:** There was a frequency of 13.6% of SD use. Most of the respondents are worried about its safety and are in favor of their regularization. Being young with high scholarship was associated with SD use.

Keywords: Central nervous system stimulants. Survey. Prevalence. Cognition. Healthy people.

Opinión y prevalencia de uso de estimulantes del sistema nervioso central en población abierta. Resultados de una encuesta electrónica

Resumen

Objetivo: Conocer la opinión y frecuencia de uso de fármacos estimulantes del sistema nervioso central (FE) en población abierta. **Métodos:** Se diseñó una encuesta anónima electrónica con 11 preguntas para conocer la frecuencia de uso de FE, su conocimiento previo, su opinión sobre los riesgos asociados con su consumo y opinión sobre su regulación, etc. La encuesta se difundió por redes sociales a > 18 años de ambos sexos. Se realizó análisis descriptivo y prueba de Chi cuadrada para buscar asociaciones entre las variables. **Resultados:** Se realizaron 526 encuestas, 271 participantes hombres (51.5%) y 249 mujeres (47.3%). La mediana de edad de 22 años (rango 18-83 años). La mediana de escolaridad fue 12 años (rango 6-20 años). 49.6% fueron estudiantes. Un 75% tenían conocimiento previo de los estimulantes, un 13.6% reporto uso previo; un 26% opino que pueden ser peligrosos; un 88% opino que deben ser controlados. La edad entre 18-30 años y la escolaridad superior a bachillerato se asoció con uso de FE. **Conclusiones:** Existió una frecuencia del 13.6% de uso de FE.

Correspondence:

*Paul Carrillo-Mora

E-mail: neuropolaco@yahoo.com.mx

2604-6180 / © 2022 Academia Mexicana de Neurología A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 06-01-2022

Date of acceptance: 21-02-2022

DOI: 10.24875/RMN.220000031

Available online: 06-05-2022

Rev Mex Neuroci. 2022;23(5):171-176

www.revexneurociencia.com

La mayoría tiene dudas sobre su seguridad y está a favor de que sean controlados. Ser joven con alta escolaridad se asoció al uso de FE.

Palabras clave: Estimulantes del SNC. Encuesta. Prevalencia. Cognición. Sanos.

Introduction

The idea of using any substance to enhance alertness or cognitive performance in healthy people is very attractive. Since decades ago, people have been using distinct drugs with this purpose, however, recently, their use in teenagers and young adults has gained a lot of popularity¹. Central nervous system stimulant drugs (SDs) are all neuroactive substances that increase certain brain neurotransmitters, in particular catecholamines (noradrenaline, dopamine, and adrenaline), although, they can increase other neurotransmitters too like serotonin, histamine, and glutamate^{1,2}. Stimulants are a diverse group of substances that include from natural molecules like caffeine, to a synthetic drug such as methylphenidate, modafinil or amphetamine, and its derivatives³.

There are a lot of publications about possible positive effects with the use of SD in alertness or cognitive functions in healthy people, however, to the date, there is no consensus about its utility as the positive observed effects continue being marginal or inconsistent between studies⁴. In spite of the lack of evidence on positive effects, its use has increased in the last years in healthy young individuals, particularly in college students^{5,6}.

In addition to the lack of evidence on its positive effects on cognition, there is a certain concern about the safety and risk of addiction to SD with repeated or chronic use⁷. Furthermore, there is an increasing controversy on the bioethical aspects related to the undiscriminated use of SD on healthy individuals, as is still in discussion if its use should be regularized by health authorities or if it should be considered a form of fraud or brain doping that must be prohibited in educational institutions and other areas⁸.

There are a great number of studies that explore the frequency of use of SD and risk factors related in healthy individuals, however, comparatively, there are few studies that have explored the public opinion on its use and regulation^{9,10}. On this matter, one study that conducted three surveys in 1400 individuals about their opinion on SD use showed that its acceptance is greater when it is reflected in other person, and also acceptance depended on the context of the use by each study¹¹. Another study performed only in medicine

students regarding the use of methylphenidate showed that more than 70% had the perception that methylphenidate could increase their cognitive performance, however, 66% of them were worried with the legality of its use and more than 90% thought that it could be dangerous for their health¹². On the other hand, a study conducted by specialists of different medical-biological and social areas showed that depending on the profession, there is great variability on the opinion about the legality of its use¹³.

Finally, although there are some studies about the frequency of use of SD in Latin America, to the best of our knowledge, there are no prior studies about the general opinion of the use of SD in this population, therefore, the objective of the present study was to get to know the opinion and frequency of the use of SD in a sample of open population in Mexico.

Method

Survey

A clinical transversal descriptive and analytic study was developed. Furthermore, an anonymous survey in an electronic format was developed, in first instance, the survey was applied in pilot group of 50 persons to evaluate the performance and reliability of each question and its adequate understanding by participants; after applying the necessary adjustments, the final version of the survey included 11 multiple-choice questions: six dichotomic answer questions (yes/no) and five with four possible responses, in addition to demographic information and other variables of the participants (sex, age, scholarship, religion, birthplace, chronic diseases, etc.). Questions explored if participants had prior knowledge on SD, if they have used any substances to enhance alertness (like caffeine or tobacco) or to enhance the cognitive functions, as well as their opinion on their safety, if these drugs should be regulated by health authorities, if they are in favor of further research, and finally, a hypothetical scenario was presented on the use of SD: where an individual uses a SD during a job examination and apparently this gives him and advantage over the other applicants obtaining at the end the job in dispute. In this context, the

Table 1. Summary of Checklist for Reporting Results of Internet E-Surveys (CHERRIES)

CHERRIE (Checklist Items)	Description
1. Design of survey	Target population: open population, adults over 18 years of age, of both sexes. Convenience sample.
2. Institutional Review Board	Research project was approved by the bioethics committee of the National Institute of Rehabilitation LGII, with registration number 54/17. The survey was conducted completely anonymous and no confidential information of the participants was managed; the informed consent for inclusion was requested in electronic format. Digital information was encrypted to guarantee confidentiality and to prevent unauthorized access.
3. Development and pre-test	Survey was developed by clinical neuroscience research experts and in first instance was applied in pilot group of 50 participants to evaluate the performance and reliability of each question.
4. Recruitment process and description of the sample having access to the questionnaire	Link for the survey (Google Forms) was sent electronically and the invitation was spread by social media in person-to-person manner, to any person who accepted to answer the survey completely, the inclusion criteria were people over 18 years old, of any gender and any residence place.
5. Survey administration	Invitation was made by social networks (WhatsApp or Facebook), participation was completely voluntary; there was no randomization in the questions; the final version included 11 multiple-choice questions: six dichotomic answer questions (yes/no) and five with four possible responses, in addition to demographic information and other variables of the participants (sex, age, scholarship, religion, birthplace, chronic diseases, etc.). Survey was applied between August 3 and November 5 of 2021.
6. Response rates	The electronic format of the survey could only be answered once, and no question could be left unanswered. No estimate of the percentage of participation was made.
7. Preventing multiple entries from the same individual	The survey was linked to a valid email address and could only be answered once per email address.
8. Analysis	Only fully answered surveys were analyzed; there was no limit of time to complete the survey and no weighting was done within the questions of the questionnaire.

participant was asked if he/she considers the situation fair or unfair and why he/she thinks the individual in the scenario got the job. These two questions have the purpose to discover their opinion on the situation from the ethical perspective.

Participants

The application of the survey had place from August 3 to November 5 of 2021. The link for the survey was sent electronically and the invitation was spread by social media to any person who accepted to answer the survey completely, the inclusion criteria were as follows: people over 18 years old, of any gender and residence place. The only exclusion criteria considered were uncompleted or repeated registered surveys. As the survey was conducted completely anonymous and no confidential information of the participants was managed, the authorization for inclusion in study was requested electronically only.

A more detailed description of the method used in the development and application of the survey is

presented in [table 1](#), following the recommendations of the Checklist for Reporting Results of Internet E-Surveys (CHERRIES)¹⁴.

Statistical analysis

The data were concentrated in a database, and in first term, descriptive statistic was used with mean, median and range to present the general characteristics of the population; in second term, a Fisher's exact test and/or a Chi-square test were used to evaluate the association between the prior use of SD and the participants demographic variables. For the analysis, the GraphPad Prism software version 6.0 was used. $p < 0.05$ was considered statistically significant.

Results

There were a total of 526 opinion surveys completed. Two hundred and seventy-one participants were male (51.5%) and 249 females (47.3%), the rest did not specify (6 = 1.1%). The average age of all participants was

29 years old (\pm 14 years). The age groups distribution was as follows: 18-20 years old: 187 (35.5%); 21-30 years old: 192 (26.5%); 31-40 years old: 46 (8.7%); 41-50 years old: 46 (8.7%); and 51-85 years old: 55 (10.4%). The average scholarship in total sample was 12.7 years (\pm 2.29 years), the distribution by school grade was as follows: elementary and middle school concluded: 47 (8.9%); high school concluded: 306 (58.1%); university concluded: 151 (28.7%); and masters or PhD: 22 (4.1%). On religion, the most frequent one was catholic in 289 participants (54.9%), other religion: 63 (11.9%), and none in 174 (33%). About place of residence, the majority was from Sinaloa (n = 264, 50.1%), 126 from Mexico City or Estado de Mexico (23.5%), and other federal entities 135 (26.6%). About their occupation: 261 were students (49.6%), workers from health areas: 41 (7.7%), other jobs: 169 (32.1%), and unemployed: 55 (10.4%). On chronic diseases, 470 (89.3%) did not suffer any chronic disease and 56 (10.6%) did.

About the prior knowledge on SD, 75.6% of participants answered yes and 24.3% answered no. On the prior use of SDs, 72 (13.6%) participants responded yes, 37 of them were male and 35 were female, from the 72 participants that answered yes, only 37 (51.3%) of them used a drug that actually possesses stimulant properties (examples: methylphenidate, Adderall, modafinil, atomoxetine, armodafinil, nicotine, and caffeine), and 38.8% mentioned used other types of drugs or substances that are not considered stimulants (examples: multivitamins, antidepressants, melatonin, and anxiolytics). On the other hand, 79% of participants (n = 416) confirmed their use of any substance (caffeine, tobacco, energy drinks, etc.) to maintain or enhance their alertness. Of them 30% (n = 125) consume it daily, 20.4% (n = 85) use it from 1 to 3 times/week and 49.5% (n = 206) consume it sporadically, 63.3% (n = 333) said "I don't know" and 10.2% (n = 54) don't answered. In the question, where participants were asked if they considered that SD should be controlled by health authorities: 463 (88%) answered positively. Finally, in the hypothetical scenario, 153 (29%) considered the scenario as "fair," 76 (14.4%) mentioned that the situation was "unfair" and 227 (63.8%) gave other responses. On the same hypothetical scenario, 54 (10.2%) participants attribute the success of person in hypothetical scenario to the use of SD and 63.8% (n = 336) attribute it to other causes different from the SD.

When performing the analysis of association of variables, three variables associated significantly with prior SD use, the age group between 18 and 30 years old (p = 0.0376), scholarship above high school (p = 0.0493),

and practicing a religion different from catholic or have no religion (p = 0.0041).

Discussion

The use of SD for different purposes has been popularized in the past few years, particularly in young and healthy individuals, however, it is difficult to establish exact reliable prevalence as there are many variables that influence the results of the studies².

In this sense, one of the aspects that limit the veracity of surveys is that the use of SD can be seen as something forbidden, dishonest, or unethical, therefore, many people usually do not tell the truth about it¹⁵. For this reason, results very important to know the opinion and attitudes of the general population toward SD use in healthy subjects. To the best of our knowledge, this is the first opinion survey on this theme conducted in our country.

In the present survey, one of the aspects to highlight about the studied population characteristics is that the majority of participants were young with an average age of 39 years old which could be due to different factors, being the most probable the easy access to electronic social media, which was the way by the survey was spread in all the age groups¹⁶. In relation to the youth of the population, we also found a very small percentage of participants with chronic diseases (10.6%). In addition, other aspect to highlight is that the education level of the included sample was high with an average of 12.7 years, which is higher than general average scholarship reported in Mexico, being it the highest in Mexico city with 12 years, and the lower in Chiapas with 8 years¹⁷. This could be due to the same reason that was previously indicated and also the fact that the great majority of our individuals were students or have a job.

About the participants responses, there was a high prevalence of previous knowledge about SD (75.6%), which could be due to the high scholarship and age of the participants, which is precisely the population where these drugs are the most popular^{1,2}. On the other hand, in spite of the high frequency of knowledge about SD, the frequency of prior use of SD for cognition was only 13.6%, however, it is difficult to contrast this number with other studies as there is a great variability in the reported prevalence, which range from 1% to 20%¹⁸. The reasons for this variability are diverse, from the way, the surveys are conducted (anonymous, electronically, personally, etc.), the type of population studied (university students, professionals, open population,

etc.), the definition of SD used, if it refers to current or previous use, if it includes the medical prescription of SD, etc.³. Other important factor to consider is that not every participant has the same concept of what is considered a SD, as the 72 participants that confirmed prior use of them, only 37 (44%) were actually using a drug that is considered a stimulant, which means that more than half of the participants attribute stimulant properties to other substances being the most common the vitamin supplements; this is highly related with the extended myth that vitamins have positive effects in alertness, energy, vitality, or even enhance the appetite¹⁹. In contrast, results interesting that 79% of individuals reported using any substance to increase or maintain alertness, being caffeine the most popular. This highlights the fact that the knowledge of “stimulant” concept is ambiguous in general population, as many people consume coffee or nicotine (both considered stimulants) as part of their daily life without pretending necessarily a specific stimulant effect²⁰. About the opinion on the safety of SD, most participants said that they could result dangerous (most think that only in excess), this opinion coincide well with previous studies that point a latent concern in users and non-users on security and risk of addiction to these drugs²¹. However, some recent clinic studies have only showed adverse effects with the moderate use of these drugs²². On the other hand, most participants (88%) confirmed to believe necessary the control and regulation of SD by health authorities, this could be due to the possible risks and ethical dilemmas that have been related to its use²¹. In practice, the majority of these drugs are sold only with medical prescription, there are some of them without this regulation like modafinil in Mexico. In spite of these concerns on the use of SD, the great majority of participants (89%), they were in favor of promote the research to develop SD more effective and safer; on this matter, we did not find other prior survey that explored the same issue, but it is possible that because the majority of the participants are young students, they are more in favor of further research son these drugs. About the ethical-hypothetical scenario presented, it is interesting that 30% considered the situation fair, however, almost 64% considered that the benefits were not related with the use of the drug. This suggests that apparently not all participants are convinced that SDs have significant effects increasing the cognitive performance in real life²³. Finally, the association analysis showed that the age group between 18 and 30 years old, a scholarship above high school, and the practice of a religion different to Catholicism or non-practicing

any religion were related factors with the prior use of SD. This profile of young high school or university students is the same profile that is related with the use of SD in the most previous studies, whereby it matches well with the reported in international literature^{2,18}. About religion, other authors have observed similar results, where the religious environment tends to associate to less use of stimulant substances, even more if they are illegal drugs²⁴. In another similar study carried out in a rural population, it was observed that religiosity was related to a lower propensity to consume illicit drugs such as cocaine and methamphetamine²⁵.

To finalize, it is very important to highlight the identified limitations and biases in the present study, being the most important the electronic distribution of the survey in social media that can sometimes be reached only by a small part of the open population (mostly young people), whereby this study cannot be totally representative of the opinion in the general population, as it was discussed before this could influence both the frequency of use and the opinions on SD; thus, in the future, it will be necessary to develop more extensive similar surveys including population above 50 years old, with more diverse levels of education and socio-economic status to be able to have a more general vision on the use and opinion about SD in healthy subjects.

Conclusion

In the present electronic anonymous survey, whose majority of participants were young adults, mainly students, a prevalence of the use of SD was 13.6%, with a frequency of 80% of the use of stimulants for alertness. Majority of participants have doubts on the safety of the stimulants, are in favor of their regulation by health authorities, but are in favor of continuing with further research on this type of drugs. Finally, the use of stimulants was associated with the age between 18 and 30 years old, a scholarship over high school and the absence of religious beliefs.

Acknowledgments

None.

Funding

The authors declare that there was no source of funding for the realization of this investigation because it was conducted by researchers own financing.

Conflicts of interest

All the authors declare that they have no conflicts of interest with this research or with the publication of its results.

Ethical disclosures

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Likewise, the authors declare that all the participants in this research gave their electronic consent for the present research and for the publication of their results anonymously.

References

1. Carrillo-Mora P, Lugo-Rodríguez Y, Franyutti-Prado KF, Rodríguez-Barragán MA, Cervera-Delgadillo NG. Stimulant drugs to promote the awake state and cognitive performance: they really work?. *Rev Mex Neurosci*. 2022 (In press).
2. Esposito M, Cocimano G, Ministrieri F, Rosi GL, Nunno ND, Messina G, et al. Smart drugs and neuroenhancement: what do we know? *Front Biosci (Landmark Ed)*. 2021;26:347-59.
3. Daubner J, Arshaad MI, Henseler C, Hescheler J, Ehninger D, Broich K, et al. Pharmacological neuroenhancement: current aspects of categorization, epidemiology, pharmacology, drug development, ethics, and future perspectives. *Neural Plast*. 2021;2021:8823383.
4. Repantis D, Bovy L, Ohla K, Kühn S, Dresler M. Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine. *Psychopharmacology (Berl)*. 2021;238:441-51.
5. Martins SS, Ghandour LA. Nonmedical use of prescription drugs in adolescents and young adults: not just a Western phenomenon. *World Psychiatry*. 2017;16:102-4.
6. Sharif S, Guirguis A, Fergus S, Schifano F. The use and impact of cognitive enhancers among university students: a systematic review. *Brain Sci*. 2021;11:355.
7. Kapur A. Is methylphenidate beneficial and safe in pharmacological cognitive enhancement? *CNS Drugs*. 2020;34:1045-62.
8. Tapia-Moreno, M.A. Cognition-enhancing drugs: bioethical implications in the light of current scientific evidence. *Bioeth Update*. 2018;4:140-53.
9. Cândido RCF, Perini E, Pádua CM, Junqueira DR. Prevalence of and factors associated with the use of methylphenidate for cognitive enhancement among university students. *Einstein (Sao Paulo)*. 2019;18:eAO4745.
10. McDermott H, Lane H, Alonso M. Working smart: the use of 'cognitive enhancers' by UK university students. *J Furth High Educ*. 2021;45:270-83.
11. Conrad EC, Humphries S, Chatterjee A. Attitudes toward cognitive enhancement: the role of metaphor and context. *AJOB Neurosci*. 2019;10:35-47.
12. Erasmus N, Kotzé C. Medical students' attitudes towards pharmacological cognitive enhancement with methylphenidate. *Acad Psychiatry*. 2020;44:721-6.
13. Ram SS, Russell B, Kirkpatrick C, Stewart K, Scahill S, Henning M, et al. Professionals' attitudes towards the use of cognitive enhancers in academic settings. *PLoS One*. 2020;15:e0241968.
14. Eysenbach G. Improving the quality of web surveys: the checklist for reporting results of internet E-surveys (CHERRIES). *J Med Internet Res*. 2004;6:e34.
15. Ram S, Hussainy S, Henning M, Stewart K, Jensen M, Russell B. Attitudes toward cognitive enhancer use among New Zealand tertiary students. *Subst Use Misuse*. 2017;52:1387-92.
16. Cope DG. Using electronic surveys in nursing research. *Oncol Nurs Forum*. 2014;41:681-2.
17. INEGI. Censo de Población y Vivienda. Mexico: INEGI; 2020.
18. Franke AG, Bagusat C, Rust S, Engel A, Lieb K. Substances used and prevalence rates of pharmacological cognitive enhancement among healthy subjects. *Eur Arch Psychiatry Clin Neurosci*. 2014;264:83-90.
19. Moreno-Rodríguez VP, Sánchez-Cabrero R, Abad-Mancheño A, Juanes-García A, Martínez-López F. Food and nutrition myths among future secondary school teachers: a problem of trust in inadequate sources of information. *Soc Sci*. 2021;10:325.
20. Samoggia A, Riedel B. Consumers' perceptions of coffee health benefits and motives for coffee consumption and purchasing. *Nutrients*. 2019;11:653.
21. Schelle KJ, Faulmüller N, Caviola L, Hewstone M. Attitudes toward pharmacological cognitive enhancement—a review. *Front Syst Neurosci*. 2014;8:53.
22. Repantis D, Bovy L, Ohla K, Kühn S, Dresler M. Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine. *Psychopharmacology (Berl)*. 2021;238:441-51.
23. Maslen H, Faulmüller N, Savulescu J. Pharmacological cognitive enhancement—how neuroscientific research could advance ethical debate. *Front Syst Neurosci*. 2014;8:107.
24. Debnam K, Milam AJ, Furr-Holden CD, Bradshaw C. The role of stress and spirituality in adolescent substance use. *Subst Use Misuse*. 2016;51:733-41.
25. Cucciare MA, Han X, Curran GM, Booth BM. Associations between religiosity, perceived social support, and stimulant use in an untreated rural sample in the U.S.A. *Subst Use Misuse*. 2016;51:823-34.

The influence of gut brain axis in neurodegenerative diseases: short review

Renata Murguiondo-Pérez¹, Óscar Vidal Alcántar-Garibay¹, Efraín Weintraub Ben-Zión¹, Enrique Blancarte-Hernández¹, Emilio Tejerina-Marion¹, Ericka Cristina Loza-López¹, Mario Galindo-Ruiz¹, and Germán Rivera-Monroy^{1,2*}

¹Centro de Investigación en Ciencias de la Salud (CICSA), FCS, Universidad Anáhuac, Huixquilucan, México, ²Department of Neurosurgery and Brain Repair, University of South Florida, Tampa, Florida, United States

Abstract

Neurodegenerative diseases (NDDs) are a global health problem that has been on the rise in recent years. Reviewing the definition of neurodegeneration, it can be established that NDDs are not only chronic diseases since acute events can also generate neurodegeneration. Recent research has focused on identifying key factors in the development of NDDs in order to generate new therapies at different levels of the pathophysiology of these diseases. The relationship between the gut microbiota and neuroinflammation has been subject of research in recent years, discovering new linking and triggering processes. In this text, we seek to summarize the existing findings regarding three NDDs (Alzheimer's disease, Parkinson's disease, and Stroke) and their relationship with the Gut Brain Axis, as well as highlight the importance of maintaining a healthy microbiota and generating therapies focused on reducing gut inflammation for the management of NDDs.

Keywords: Neurodegeneration. Gutbrain axis. Alzheimer. Parkinson. Stroke.

La influencia del eje intestino-cerebro en las enfermedades neurodegenerativas: breve reseña

Resumen

Las enfermedades neurodegenerativas son un problema de salud mundial que ha ido en aumento en los últimos años. Revisando la definición de neurodegeneración, se puede establecer que las enfermedades neurodegenerativas no son solo enfermedades crónicas, ya que los eventos agudos también pueden generar neurodegeneración. Investigaciones recientes se han centrado en identificar factores clave en el desarrollo de enfermedades neurodegenerativas para generar nuevas terapias a diferentes niveles de la fisiopatología de estas enfermedades. La relación entre la microbiota intestinal y la neuroinflamación ha sido objeto de investigación en los últimos años, descubriendo nuevos procesos de vinculación y desencadenantes. En este texto buscamos resumir los hallazgos existentes respecto a tres enfermedades neurodegenerativas (Alzheimer, Parkinson y Stroke) y su relación con el Eje Intestino Cerebro, así como resaltar la importancia de mantener una microbiota saludable y generar terapias enfocadas a reducir inflamación para el manejo de enfermedades neurodegenerativas.

Palabras clave: Neurodegeneración. Eje intestino cerebral. Alzhéimer. Parkinson. Ataque.

Correspondence:

*Germán Rivera-Monroy

E-mail: german.riveramo@anahuac.mx

Date of reception: 13-05-2021

Date of acceptance: 07-02-2022

DOI: 10.24875/RMN.21000821

Available online: 19-10-2022

Rev Mex Neuroci. 2022;23(5):177-182

www.revexneurociencia.com

2604-6180 / © 2022 Academia Mexicana de Neurología A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Neurodegenerative diseases (NDDs) are characterized by a progressive dysfunction and loss of vulnerable neurons and are the leading cause of disability and morbidity worldwide¹. Neuronal cell death is the final outcome when multiple chronic and progressive stressors pile up beyond the neuron's recovery capacity, resulting in neurodegeneration². However, a traumatic incident or acute event like stroke can cause a sudden decline of energy and a pro-inflammatory environment in the affected neurons, which also results in acute cell death and brain tissue degeneration². Thus, we can conclude that NDDs are not strictly chronic neuronal death pathologies, but also involve acute processes.

The gut-brain axis (GBA) refers to the set of biological systems which creates a network connection that allows bidirectional communication between gut microbiota and diverse areas on the brain and the SNC³. GBA interconnection routes such as the vagus nerve, the immune system, the hypothalamic-pituitary-adrenal axis (HPA), tryptophan metabolism, and the enteric nervous system⁴. When there is an aberrant response from the normal microbiota or it has suffered a number of alterations, an inflammatory response takes place, resulting in the liberation of cytokines and microbial metabolites which can lead to a certain level of neuroinflammation⁵.

Gut microbiome plays a crucial role in neurodevelopment, as well as in several brain diseases⁶. Intestinal microorganisms have an impact on the host's metabolism and immune status, which affects neuronal pathways in the enteric and central nervous systems³. Moreover, it has been recently demonstrated that poor communication between gut-brain axis networks as well as gut microbiota disturbance can lead to gut inflammation disorders, and consequently alter cognitive functions, favoring the development of acute and chronic neurodegenerative conditions⁷. In this text, we aim to describe the influence of GBA in three specific neurodegenerative pathologies (Stroke, Alzheimer's disease [AD], and Parkinson's disease [PD]), as well as highlight the importance of healthy GBA status as possible preventive and active treatment for NDDs.

Alzheimer

AD represents a multifactorial slowly and progressive neurodegenerative disorder characterized by a progressive cognitive decline as well as by a gradual impairment in emotion, language, and memory⁸. It

represents the leading cause of dementia worldwide⁹. According to Mexico's National Institute of Neurology and Neurosurgery, AD's prevalence is around 350,000 people, of which 2,030 die each year. The lack of official data by the Mexican health system makes it difficult to elucidate other statistics related to this disease, however, a work carried out by Gutierrez-Robledo and Arrieta-Cruz in 2015¹⁰, shows that AD has an incidence of 27.3 (1000 people/year) and a greater predisposition for women over 60 years of age.

The pathogenic hallmarks of AD include extracellular aggregates of amyloid β ($A\beta$) plaques and intracellular accumulation of neurofibrillary tangles (NFTs), composed of the hyperphosphorylated tau protein¹¹. Abnormal cleavage of the $A\beta$ precursor protein, a membrane integral protein, by secretase enzymes⁵, results in the formation of insoluble $A\beta$ fibrils, which are then excreted into the interstitial fluid and start to oligomerize and aggregate into plaques, diffusing into synaptic clefts and thus interfering with normal synaptic signaling^{11,12}. $A\beta$ aggregates begin to form in the neocortex and appear later in the hippocampus⁴. The tau protein is widely distributed throughout neurons in association with microtubules, playing a critical role in cytoskeletal integrity and axonal transport¹³. Polymerization of $A\beta$ fibrils, in turn, leads to abnormal activation of several kinases, causing hyperphosphorylation of tau and a subsequent polymerization into insoluble NFTs²¹. The typical clinical course of AD can be divided into 4 stages. AD symptoms usually develop once both $A\beta$ and tau aggregates are found in the neocortex^{12,14,15}.

AD remains being one of the diseases with the lowest number of pharmacological therapeutic options. As of date, the first-line treatment option for AD remains to be cholinesterase inhibitors, including donepezil, galantamine, and rivastigmine^{15,16}. As of June 2021, a new drug option received FDA approval for AD treatment: Aducanumab (Aduhelm™)^{17,18}, a human gamma immunoglobulin 1 monoclonal antibody targeted against $A\beta$, which should be initiated in the early stages of the disease, when the patient's cognitive impairment is still mild¹⁷, however, it's long-term tolerability and security is currently under evaluation in a multinational phase 3b clinical study.

Parkinson

PD; one of the most common and intricate neurological disorders in clinical medicine, is a progressive NDD caused by a dopamine deficiency throughout basal ganglia, secondary to the premature death of

dopaminergic neurons in the substantia nigra pars compacta. Resulting in a movement disorder with marked parkinsonian motor symptoms¹⁸. Although there is a gap in the epidemiological information of PD in Mexico, there have been estimations for a prevalence of 40-50 cases/100,000 inhabitants a year, additionally, it's reported to be the fourth cause of consultation in the National Institute of Neurology and Neurosurgery¹⁹.

Globally, PD represents the second most common neurodegenerative disorder²⁰, caused by multifactorial etiology that combines environmental and genetic factors, however, its presentation is linked to specific disease hallmarks, firstly, a degeneration of dopaminergic neurons in the substantia nigra, recent studies have shown that loss of the dopaminergic terminals in the striatum directly correlates with motor symptoms onset. And secondly, sporadic PD pathognomonic intraneuronal aggregates known as Lewy bodies and neurites²¹: eosinophilic cytoplasmic inclusion bodies with abundant alpha synuclein²⁰, located in first stage pathology medulla oblongata that consequently spread through neural pathways to the substantia nigra in latter phases. There are genetic factors related to the pathogenesis of PD, with roles in mitophagy, protein degradation, increase kinase activity, the key genes being: PARKIN, PINK1, DJ-1, LRRK2, and GBA²¹. As a result of such pathogenesis, PD presents motor and nonmotor symptoms. Classical motor findings list resting tremor (often unilateral), postural instability, rigidity, and bradykinesia, furthermore, speech turns softer, swallowing gets affected, sialorrhea and difficulty rising from a chair might present due to the slowing of movement, whereas nonmotor symptoms include cognitive decline, sleep disturbances, dysautonomia, anosmia and even psychological and gastrointestinal alterations such as anxiety, depression, nausea, bloating and abdominal discomfort²².

Currently, there is no curative treatment for PD, thus, it focuses on decreasing the degree of any symptoms developed by the patient. The best treatment plan includes levodopa administration, the immediate precursor of dopamine²⁰.

Stroke

Stroke accounts for the second leading cause of death²¹. It is defined as a neurological event in which abrupt impairment of blood perfusion through cerebral vessels to the brain accounts for a neurological outburst²². In Mexico, stroke does not only represent an

important source of disability and mortality for its population but a great threat to family conformation and dynamics²³. Epidemiological information suggests a rise in the prevalence of stroke, in 2008 stroke scaled up from the fourth cause of general mortality (2000) to the third with more than 30,000 deaths in that year²⁴. After analyzing verified stroke cases in 2011, estimations were made, it was concluded that the prevalence was 5.1 every 1000 inhabitants while the accumulated incidence showed 232.3/100,000²³.

Stroke can be divided into ischemic and hemorrhagic, with the ischemic variant accounting for the vast majority of cases²⁵. The ensuing insufficient cerebral blood flow and the subsequent lack of oxygen supply to the brain leads to cell death by various mechanisms such as ionic imbalances (calcium overload), glutamate excitotoxicity, bloodbrain barrier breakdown, activation of microglia with the subsequent neuroinflammation, cytotoxic and vasogenic edema, dysregulation of energy metabolism and oxidative stress²¹, leading ultimately to necrosis of the cerebral parenchyma. It has been recognized that Stroke harmful effects consist of two principal injuries First injury alludes to the direct effects of ischemia and necrosis to brain tissue, second injury refers to the deleterious effects of persisting neuroinflammation several days after the stroke took place, this persisting inflammatory response might be active even months apart from the onset event²⁶. Necrosis and apoptosis-mediated cell death drive an inflammatory reaction, in which innate and adaptive immune cells release a large amount of proinflammatory cytokines, such as tumor necrosis factor-alpha, interleukin (IL) 1 beta, IL-6, and interferon-gamma, which exacerbate the initial damage, manifested by a larger ischemic area and a worsening of symptoms in patients²⁷. In addition, there is an activation of microglia and astrocytes by the presence of inflammatory mediators²⁸.

Clinical manifestations in stroke patients vary in presentation, severity, and structure due to variables such as onset, affected area, and etiology, thus, it's identification and diagnosis can be misleading and complicated for physicians²⁶, nevertheless, an acute onset of signs like hemiparesis, aphasia^{26,29}, gait disturbances, eye movement abnormalities, visual field abnormalities and symptoms such as subjective weakness, paresthesia, headache and dizziness with additional focal neurologic deficit may assist examiners in the early recognition of a patient developing a stroke²⁹.

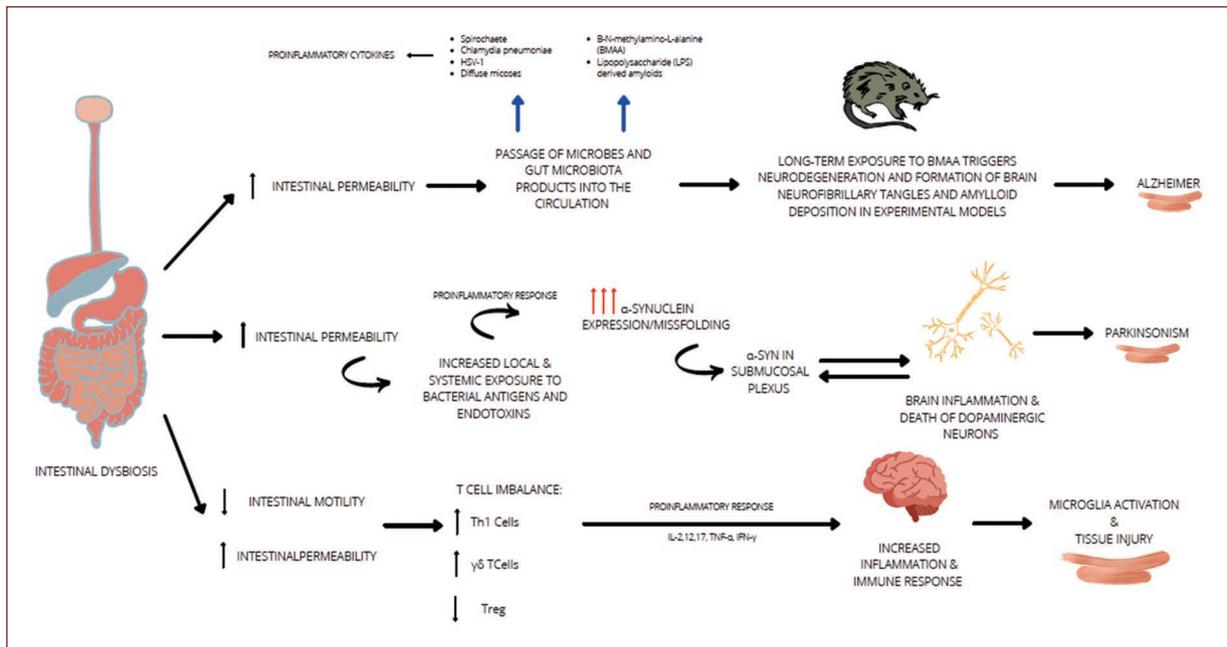


Figure 1. GBA dysbiosis influence over neurodegenerative diseases, specifically Alzheimer’s disease, Parkinson’s disease and stroke.

GBA and NDDs

Microbiota is a symbiotic population of bacteria, viruses, fungi, and other microorganisms that coexist in the gastrointestinal tract³⁰. The question remains “how can microbes in the gut have an effect in the brain?” There are many potential linking pathways, such as the autonomic nervous system connecting through the 10th cranial nerve, the vagus, (specifically the hepatic and celiac branches) the gut, and the brain with neuronal and neuroendocrine signals bidirectionally³¹. Other pathways involve the HPA, altering the microbiota in stressful situations by releasing molecules such as norepinephrine, catecholamines, serotonin, and cytokines in the enterochromaffin cells in the gut, short-chain fatty-acids transported to the brain in the vagus nerve and/or the systemic circulation, stimulating the neurons, microglia, astrocytes, and bloodbrain barrier³².

As summarized in Figure 1, neurological disorders, especially those presenting with neurodegeneration, have been associated with harmful environmental factors identified in childhood; in particular, an unbalanced diet that alters early gene expression leads to epigenetic changes that manifest in adulthood. Research suggests that Gut dysbiosis increases gut permeability causing a bacterial leak that triggers an inflammatory response. Proinflammatory cytokines are released, which increases the blood-brain barrier permeability,

inducing neuroinflammation³². It’s known that common bacteria present in the gut microbiota such as Lactobacillus, Bifidobacteria, Enterococcus, and Streptococcus species produce neurotransmitters like acetylcholine, GABA, and serotonin in a high scale, for example, 90% of the serotonin for brain and gastrointestinal tract use is produced in the gut^{31,32}. This is important because serotonin binding to 5-HT receptors on microglia induces the release of cytokine-carrying exomes, therefore modulating a gut-induced neuroinflammation⁵.

GBA and AD

The mechanisms of the brain-gut-microbiota axis related to the pathogenesis of stress conditions or brain disorders are being discovered. Inflammation and Alzheimer disease have been studied for their relation, due to the increased amyloid deposition under inflammatory conditions. Microbiome studies point out that a variety of microbial species, including *Enterobacteriaceae* and *Lactobacillaceae* families generate significant quantities of functional amyloid³³. These microbial species increase on the gut as the human gets older, and with them, the quantity of functional amyloid³⁴. Amyloid neurotoxic properties make older people more susceptible to gut dysbiosis, and because of the GBA it is suggested that it can increase the risk of developing AD^{33,34}.

Over the last years, several studies have identified that the group of bacteria mentioned above, may also produce damage to gut epithelium, which increases its permeability and the leak of bacteria to the blood system³⁴. Gut microbiota or toxic metabolites can then travel to the brain and, under other proinflammatory conditions or immune system depression (like the physiological immune system capabilities reduction that occurs in the elder) penetrate the bloodbrain barrier and induce neuroinflammation. Nevertheless, more research is needed in order to identify specific bacteria or metabolites that might be involved in AD pathophysiology³⁵.

GBA and PD

The pathogenic mechanisms underlying neurodegenerative disorders such as PD is attributable to multifactorial changes. Emerging data has confirmed that imbalances on the GBA trigger or exacerbate the progression of PD³⁶. An important hallmark on PD is the α -synuclein (aSyn). aSyn is a protein consisting of 140 amino acids that play an important role on synaptic plasticity and interact with presynaptic vesicles. Several research studies have studied the aSyn aggregates in the GI tract. Phosphorylated aSyn deposition has been observed on subjects with idiopathic rapid eye movement sleep behavior disorder, a prodromal marker of PD, as well in gastric, duodenal, and colonic biopsies undertaken by PD patients before the presentation of motor signs^{37,38}.

The innate immune system, the first line of defense against invading microbes, can sense the presence of microorganisms through a number of pattern-recognition receptors (PPRs), which recognize pathogen-associated molecular patterns. Among the different PPRs, Toll-like receptors (TLRs) stand out on PD and GBA relations. TLR-4 has appeared in several studies interacting with aSyn, triggering microglial responses^{38,39}.

An existing hypothesis suggests that the vagus nerve is a potential pathway of retrograde transport of aSyn between the enteric nervous system and the brain. Enteric dysregulation can contribute to PD pathogenesis due to the increase on intestinal epithelial barrier permeability⁴⁰. The association between inflammatory bowel disease and PD can be another role of the intestinal inflammation. Alteration on PD patient's microbiomes has shown decreased abundance of genus *Prevotella*, *Roseburia* and *Blautia* genera, *Lachnospiraceae* family, among others, and an important increase

on *Lactobacillaceae* family⁴¹. With this new perspective focusing on the microbiome, PD can have a new understanding, providing new therapeutic approaches involving the GBA.

GBA and ischemic stroke

Existing evidence has shown how ischemic stroke is capable of causing an alteration on the gut microbiota. After stroke, an inflammatory response takes place principally induced by DAMPs and cytokines release²⁸. BBB suffers damage and a bidirectional communication with gut microbiota enhances the immune response. The changes in BBB allow inflammatory and immune cells from the circulation to get into the brain parenchyma, which interacts with innate immune cells in the CNS. Furthermore, gut inflammation (initially induced by the stroke) can confer systemic inflammation that contributes to brain inflammation^{28,29}.

Direct neural inflammation produced by the ischemic event, with the addition of systemic inflammation due to microbiota dysbiosis potentially enhances the harmful effects of stroke and increases final neurodegeneration of the secondary injury. Similarly, recent research indicates that pro-inflammatory gut microbiomes may be related to worst prognosis after stroke likely due to a heightened immune system that generates detrimental pro-inflammatory response after cerebral ischemia⁴².

Novel therapies targeting microbiota induced neuroinflammation are being developed⁴³. The inhibition of intestinal IL-17 secreting $\gamma\delta$ T-cells by Treg cells may reduce poststroke inflammation in mice⁴⁴. Th17 cells are used at a significant part in keeping mucosal barrier, inflammation, and microbial translocation in the gut and have the capacity to efficiently break the BBB to penetrate in the CNS. Inhibition of Th17 cytokines may be chosen to reduce inflammation⁴⁴. The novel transgenic models can help for the identification of the origin, the mission, and fate of gut migrating immune cells in stroke.

Conclusion

NDDs have a strong relationship with gut microbiota in their pathophysiology. Inflammation appears to be a constant link between the gut and brain that encourages the development of these diseases. GBA is a field of study that must be deeply analyzed in order to better understand NDDs and to be able to propose new therapies that help not only to treat but also prevent NDDs.

Funding

This research has not received any specific grant from agencies of the public, commercial, or non-profit sectors.

Conflicts of interests

The authors declare no conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

- Gabor GC. Concepts and classification of neurodegenerative diseases. *Handb Clin Neurol.* 2017;145:301-7.
- Chi H, Chang HY, Sang TK. Neuronal Cell death mechanisms in major neurodegenerative diseases. *Int J Mol Sci.* 2018;19:3082.
- Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-gut-microbiome axis. *Cell Mol Gastroenterol Hepatol.* 2018;6:133-40.
- Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome-gut-brain axis. *Gut Microbes.* 2019;10:555-68.
- Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. *Nat Neurosci.* 2017;20:145-55.
- Benakis C, Martin-Gallausiaux C, Trezzi JP, Melton P, Liesz A, Wilmes P. The microbiome-gut-brain axis in acute and chronic brain diseases. *Curr Opin Neurobiol.* 2020;61: 1-9.
- Breit S, Kupferberg A, Rogler G, Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. *Front Psychiatry.* 2018;9:44.
- Soria-Lopez JA, González HM, Léger GC. Alzheimer's disease. *Handb Clin Neurol.* 2019;167:231-55.
- Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. *F1000Res.* 2018;7:F1000 Faculty Rev-1161.
- Gutiérrez-Robledo LM, Arrieta-Cruz I. Dementia in Mexico: the need for a national Alzheimer's plan. *Gac Med Mex.* 2015;151:620-5.
- Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *Int J Nanomed.* 2019;14:5541-54.
- Hane FT, Lee BY, Leonenko Z. Recent progress in Alzheimer's disease research, Part 1: pathology. *J Alzheimers Dis.* 2017;57:1-28.
- Dhillon S. Aducanumab: first approval. *Drugs.* 2021;81:1437-43.
- Chen YG. Research progress in the pathogenesis of Alzheimer's disease. *Chin Med J (Engl).* 2018;131:1618-24.
- Brejijeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules.* 2020;25:5789.
- Fillit H, Green A. Aducanumab and the FDA where are we now? *Nat Rev Neurol.* 2021;17:129-30.
- Kalia LV, Lang AE. Parkinson's disease. *Lancet.* 2015;386:896-912.
- Trejo-Ulibarri HM, Solís-S JC. Advances in the identification of early biomarkers in Parkinson's disease. *Rev Med MD.* 2018;9:163-9.
- Hayes MT. Parkinson's disease and parkinsonism. *Am J Med.* 2019; 132:802-7.
- Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. *Clin Geriatr Med.* 2020;36:1-12.
- Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. *J Clin Invest.* 2020; 130:2777-88.
- Torres-Arreola LD, Valenzuela-Flores AA, Villa-Barragán JP. Characterization of stroke patients attended at IMSS hospitals in Mexico City. *Rev Med Inst Mex Seguro Soc.* 2018;56:18-25.
- Sifat AE, Vaidya B, Villalba H, Albekairi TH, Abbruscato TJ. Neurovascular unit transport responses to ischemia and common coexisting conditions: smoking and diabetes. *Am J Physiol Cell Physiol.* 2019;316:C2-15.
- Maida CD, Norrito RL, Daidone M, Tuttolomondo A, Pinto A. Neuroinflammatory mechanisms in ischemic stroke: focus on cardioembolic stroke, background, and therapeutic approaches. *Int J Mol Sci.* 2020;21:6454.
- Sun J, Chi L, He Z, Gao Y, Gao Y, Huang Y, et al. NLRP3 inflammasome. *J Drug Target.* 2019;27:866-75.
- Campbell BC, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, et al. Ischaemic stroke. *Nat Rev Dis Primers.* 2019;5:70.
- Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA. Neuroinflammation: friend and foe for ischemic stroke. *J Neuroinflammation.* 2019;16:142.
- Pluta R, Januszewski S, Czuczwar SJ. Neuroinflammation in post-ischemic neurodegeneration of the brain: friend, foe, or both? *Int J Mol Sci.* 2021;22:4405.
- Stonesifer C, Corey S, Ghanekar S, Diamandis Z, Acosta SA, Borlongan CV. Stem cell therapy for abrogating stroke-induced neuroinflammation and relevant secondary cell death mechanisms. *Prog Neurobiol.* 2017;158:94-131.
- Kimono DA. Gastrointestinal problems, mechanisms and possible therapeutic directions in Gulf war illness: a mini review. *Military Med Res.* 2021;8:50.
- Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaansen TF, Boehme M, et al. The Microbiota-gut-brain axis. *Physiol Rev.* 2019;99:1877-2013.
- Sun LJ, Li JN, Nie YZ. Gut hormones in microbiota-gut-brain crosstalk. *Chin Med J.* 2020;133:826-33.
- Sun M, Ma K, Wen J, Wang G, Zhang C, Li Q, et al. A review of the brain-gut-microbiome axis and the potential role of microbiota in Alzheimer's disease. *J Alzheimers Dis.* 2020;73:849-65.
- Rutsch A, Kantsjö JB, Ronchi F. The gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology. *Front Immunol.* 2020;11:604179.
- Matej R, Tesar A, Rusina R. Alzheimer's disease and other neurodegenerative dementias in comorbidity: a clinical and neuropathological overview. *Clin Biochem.* 2019;73:26-31.
- Bullich C, Keshavarzian A, Garssen J, Kraneveld A, Perez Pardo P. Gut vibes in Parkinson's disease: the microbiota gut brain axis. *Mov Disord Clin Pract.* 2019;6:639-51.
- Schaeffer E, Kluge A, Böttner M, Zunke F, Cossais F, Berg D, et al. Alpha Synuclein connects the gut-brain axis in Parkinson's disease patients: a view on clinical aspects, cellular pathology, and analytical methodology. *Front Cell Dev Biol.* 2020;8:573696.
- Stockholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological α -synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. *Ann Neurol.* 2016;79:940-9.
- Kam TI, Hinkle JT, Dawson TM, Dawson VL. Microglia and astrocyte dysfunction in Parkinson's disease. *Neurobiol Dis.* 2020;144:105028.
- Sprenger FS, Stefanova N, Gelpi E, Seppi K, Navarro-Otano J, Offner F, et al. Enteric nervous system α -synuclein immunoreactivity in idiopathic REM sleep behavior disorder. *Neurology.* 2015;85:1761-8.
- Boertien JM, Pereira PA, Aho VT, Scheperjans F. Increasing comparability and utility of gut microbiome studies in Parkinson's disease: a systematic review. *J Parkinsons Dis.* 2019;9:S297-312.
- Lee J, D'Aigle J, Atadja L, Quaiocoe V, Honarpisheh P, Ganesh BP, et al. Gut microbiota-derived short-chain fatty acids promote poststroke recovery in aged mice. *Circ Res.* 2020;127:453-65.
- Arya AK, Bingren H. Brain-gut axis after stroke. *Brain Circ.* 2018;4:165-73.
- Mo Y, Sun YY, Liu KY. Autophagy and inflammation in ischemic stroke. *Neural Regen Res.* 2020;15:1388-96.

Aspects of neurodevelopment between autism spectrum disorders and epilepsy

Paola Núñez-Contreras¹, Daniela Granado-Rocha¹, Maritza Carvajal-Game², and Ana M. Torres-Perez²

¹Hospital Doctor Exequiel González Cortés, ²Unidad Docente Neurología Pediátrica. Universidad de Santiago de Chile. Chile

Abstract

There are high incidences of epilepsy and autism in the preschool and school ages, in which the synaptic plasticity and synaptogenesis are more active, a primary interruption of the synaptic function due to injury or genetic mutation may result in the appearance of both pathologies as in Lennox Gastaut S., De Aircadi S, epilepsy with continuous slow waves during sleep and Landau Kleffner S. There is evidence of abnormal brain maturation in autism spectrum disorders (ASD). Normal pruning eliminates faulty connections and optimizes neuronal functioning. In autism, this pruning would result in degrees of anatomical “over-connectivity” that increases or decreases the efficiency of communication between cortical regions. The same occurs with axonal myelination that affects integrated interregional cortical communication and synchronization. Critical and vulnerable mechanisms are appreciated during the peri-neonatal period, with subsequent stabilization of the synapses to form pre-designed neural networks through genetic mechanisms and modified by environmental factors. There are anomalies in different proteins that modulate the first phase of synaptogenesis, mutations in protocadherins, cadherins, and abnormalities in glutamatergic and GABAergic systems that affect the brain. All these aspects are critical for learning, language, and memory in both autism and epilepsy.

Keywords: Synaptogenesis, Autism, Epilepsy.

Aspectos del neurodesarrollo entre trastornos del espectro autista y epilepsia

Resumen

Se presentan altas incidencias de epilepsia y autismo en el preescolar y escolar, edades en las que la plasticidad sináptica y sinaptogénesis es más activa, una interrupción primaria de la función sináptica por lesión o mutación genética puede resultar en aparición de ambas patologías como en S. Lennox-Gastaut, S. De Aircadi, Epilepsia con ondas lentas continuas durante el sueño y el S. de Landau Kleffner. Existe evidencia de maduración anormal del cerebro en TEA. La poda normal elimina conexiones defectuosas y optimiza el funcionamiento neuronal. En autismo, esta poda daría lugar a grados de “sobreconectividad” anatómica que aumentan o disminuyen la eficiencia de la comunicación entre regiones corticales. Igual ocurre con la mielinización axonal que afecta la comunicación cortical interregional integrada y sincronización. Mecanismos críticos y vulnerables durante el período peri-neonatal, con posterior estabilización de las sinapsis para constituir redes neuronales prediseñadas mediante mecanismos genéticos y modificadas por factores ambientales. Existen anomalías en diversas proteínas que modulan la primera fase de la sinaptogénesis, mutaciones en las protocadherinas, cadherinas y

Correspondence:

*Paola Núñez-Contreras,
E-mail: paolagnc@gmail.com

Date of reception: 08-06-2020

Date of acceptance: 29-04-2021

DOI: 10.24875/RMN.20000055

Available online: 16-06-2022

Rev Mex Neuroci. 2022;23(5):183-191

www.revexneurociencia.com

2604-6180/ © 2021 Academia Mexicana de Neurología A.C. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

anomalías en sistemas glutamatergicos y gabaérgicos que afectan el cerebro. Todos estos aspectos son críticos para el aprendizaje, lenguaje y memoria tanto en autismo como epilepsia.

Palabras clave: Sinaptogenesis, Autismo, Epilepsia.

Introduction

The association between autism spectrum disorders (ASD) and epilepsy has been established in numerous studies. The rate of epilepsy in children diagnosed with ASD is described by 30%, meaning that one in every three patients with autism will develop epilepsy during their lifetime¹.

If children with a diagnosis of autism and without epilepsy symptoms have an electroencephalography (EEG), 10% would have an EEG with epileptic form activity. These anomalies remain over time, continuing in adolescents and young adults with autism² (Giovannardi Rossi, 2000). A relationship between the regression of language and epilepsy is associated, and the epileptic form alterations found when performing longer electroencephalographic records.

In rare cases, epilepsy may be responsible for autistic traits, such as in acquired epileptic aphasia, where marked impairment of social communication has been described as autistic, but apparently this is a direct result of epilepsy³. To the question of whether autism causes epilepsy, it is argued that autism could cause epilepsy on the basis that, frequently, autism is associated with another comorbid cerebral dysfunction, especially intellectual deterioration, which is also associated with epilepsy. This coexistence of autism and epilepsy is an association, not causation³.

The purpose of this review is to describe the different relational elements shared between ASD and epilepsy, as brain mechanisms, which include the regulation of gene transcription, cell growth, synaptogenesis, and the role of glutamatergic and GABAergic systems. It should also be taken into consideration that there are also metabolic, mitochondrial, and genetic defects that underlie ASD and epilepsy.

Methods

Bibliographic search in PubMed, ScienceDirect, Springer Link, Cochrane, textbooks, referring to Epilepsy, Autism and Neurodevelopment, 70 articles were found, only five establish a relationship between them; it is for this reason that we consider it important to review this relationship.

Autism background

Leo Kanner, in 1943, described the autistic disorder, now called ASD⁴, where deficiencies are found in socio-emotional reciprocity, deficiencies in non-verbal communicative behaviors, used in social interaction, deficiencies in the development, maintenance, and understanding of relationships, in addition to restrictive and repetitive patterns of behavior, interests, and activities; symptoms that must be present from the earliest stages of development⁵. Associated with these, there are serious impairments in the ability to relate, adapt and interact socially, as well as in neurocognitive development¹⁻⁶.

ASDs can occur with or without medical, genetic, neurodevelopmental, mental, or behavioral disorders. Together, they have a prevalence of 0.6% in the general population⁷. The estimated prevalence of ASD was 2.24% (1 in 45), in 2014, established by Centers for Disease Control⁸.

According to the Ministry of Health of Chile, it is estimated that for 240,569 live births registered in 2007 (DEIS), the approximate number of people diagnosed with ASD in Chile was 2156 children (1 in 111) five according to the Department of Statistics and Information of Health of the Ministry of Health. Fombonne et al. (2016) determined the prevalence of autism in Mexico, concluding that 1 in every 115 children would have this disorder⁵.

Biological mechanisms described in autism

Considering autism a neurodevelopmental disorder, there is an abnormal maturation of the brain^{9,10}. In the normal brain, initial growth, neuronal loss, and synaptic pruning are timed so that activity and experience support the organization of functional networks (Kandel et al., 2000)¹¹. While normal pruning could help eliminate faulty connections and optimize coordinated neuronal functioning, pruning in autism would possibly result in some degree of anatomical “over-connectivity” that could increase or decrease the efficiency of communication between cortical regions. In autism, the absence of neuronal structures, including apoptosis, axonal pruning and dendritic degeneration, as well as increased neurogenesis, would explain the autism clinic, in combination with specific genetic alterations.

Lewis and Elman (2008)¹² postulate that the abnormalities in these maturation processes are consistent with the findings of increased brain size in autism in the early stages of development, the largest increase being in the frontal cortex. A compensatory process that would reduce the functional impact of the increase in brain size would be a reduction in the proportion of long-distance connections.

Adam et al. (2012)⁹ propose a lack of integrity of the tracts of the white matter that carry information between the different brain regions, affecting the interregional cortical communication. Another mechanism affected is the myelination of axons that also affect integrated interregional cortical communication and synchronization.

Geschwind and Levitt (2007)¹⁰ express that biological mechanisms affect connectivity; several microstructural processes could explain the impediments in the functional and anatomical connectivity observed in autism. A series of initial processes of neurodevelopment, such as neuronal migration and the establishment of synapses, could individually or in combination lead to anomalies in the development of connectivity.

Herbert et al. (2004)¹³ suggest that the corpus callosum is usually smaller in autism, this decrease in size could be an index of white matter deficit that could contribute to damage cortical connectivity. Vargas et al. (2005)¹⁴ found evidence of astroglial and microglial activation and neuroinflammation in the gray and white matter (in samples taken from the middle frontal gyrus, anterior cingulate gyrus and posterior cerebellar hemispheres) and the symmetry of the temporal planes in postmortem case studies.

Alterations in synaptogenesis and autism

Juan-Jose García-Peñas et al. (2012)¹⁵ conducted a review on alterations of synaptogenesis in autism; it is known that the first functional synapses in the human brain are evident from the 40th day of embryonic life and later undergo a complex process of structural and functional maturation. These mechanisms are especially critical and vulnerable during the perinatal and neonatal period, then there is stabilization of the synapses to constitute pre-designed neural networks through genetic mechanisms and modified by environmental factors.

Suda et al. (2011)¹⁶ described histochemical studies in brains of autistic children and adolescents, where anomalies have been revealed in various proteins that modulate the first phase of synaptogenesis, including ephrins type EFNA4 and EFNB3, plexin PLXNA4, and

ROBO2 and ROBO3 (roundabout 2 and 3), mainly in the primary motor cortex and the anterior cingulate cortex.

SynCAM1 (membrane protein of the Ig superfamily) that functions as an adhesion molecule is located symmetrically in both membranes of the synapses and binds to them through an extracellular domain to form a homophilic component of cell adhesion. Zhiling (2008) described missense mutations in the SynCAM1 gene in autistic people.

N-cadherin (CDH2) acts as a basic adhesion molecule for the development of excitatory and inhibitory synapses, protocadherins are essential in the development of synaptic specificity. Morrow and Bhalla (2008) described mutations in the protocadherins PCDH9 and PCDH10 and in cadherins CDH15 and CDH18 in subjects with autism and mutations in protocadherin PCDH8, which interacts with the kinase TAO2 (serine/threonine-protein kinase TAO2) and MAPK3 (mitogen-activated protein kinase 3), which map in the region 16p11.2, one of the most important loci of susceptibility for autism, this alteration of PCDH8 would produce an internalization of the synaptic receptors AMPA, which would modify the normal development of the synapses.

Glutamatergic-GABAergic systems and autism

The glutamatergic and GABAergic systems are important foci of pathology in the brain of patients with autism. Many investigations stand out the deregulation of several proteins involved in this pathway (Fatemi et al., 2012)¹⁷.

The GABA A receptors are responsible for the mediation of rapid inhibitory action of GABA in the brain. GABA B receptors play an important role in maintaining an excitatory/inhibitory balance in the brain. The GAD protein is responsible for the conversion of Glutamate to GABA. It has been shown that GAD 65 and 67 are reduced in the cerebellum of adults with autism. In the cerebellum, concordant reductions have been observed in mRNA and in the protein levels of GABA R1 receptor in adults with autism¹⁸.

Concurrent reductions were also observed in GABA A and GABA B receptors in Brodmann areas 40 and 9, decreased densities of the GABA A receptors in the anterior cingulate cortex and GABA B in the fusiform gyrus.

Reelin (serine protease of the extracellular matrix) is expressed in the GABAergic and glutamatergic cells; regulates the lamination of neurons during embryonic

development; and helps in the processes of neuronal migration in the early development, modulation of synaptic plasticity throughout life, and maintenance of long-term potentiation.

Many studies have shown abnormal expression of reelin in autism and reproduced these results evidencing polymorphisms of the RELN gene, decreased reelin mRNA in the upper frontal cortex and cerebellum, and decreased expression of Reelin in blood analyzes¹⁹. Reelin also binds to very low-density lipoprotein (VLDLR) receptors, apolipoprotein receptor 2, and $\alpha 3\beta 1$ integrin. Through these, it is capable of activating Dab-1 (Disabled-1), an intracellular adapter protein that facilitates the signal between the reelin-secreting cells and the pyramidal cells. VLDLR is upregulated in the upper frontal cortex and cerebellum of adult patients with autism, while Dab-1 is significantly reduced in these areas, suggesting the alteration of signaling in the reelin pathway.

Epilepsy background

According to the ILAE 2017, epileptic seizure is defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”²⁰. It is the clinician’s first task to determine that an event has the characteristics of a seizure and not one of the many imitators of seizures. The next step is classification into a seizure type, the electroclinical syndrome, and determine the treatment consistent with the pathophysiological mechanisms of each of the different epilepsies²¹.

The epidemiology varies according to the underdeveloped or developed countries, being the average in developed countries of 5.8/1000 habitants, while in low-resource countries, it is 10.3/1000 in urban areas and 15.4/1000 in rural areas²².

In high-income countries, incidence rates in the general population are between 30 and 50/100,000 people. In low- and middle-income countries, this figure can be up to twice as high²³. In Mexico, the prevalence in the centers of the Priority Epilepsy Program is 11.4-20.3/1000 (2004)²⁴. In Chile, the prevalence of epilepsy is 10-17.7 × 1000 (Lavados et al.)²⁵.

Epileptogenesis

Epileptogenesis is the process by which the previously normal brain is functionally altered and biased toward the generation of abnormal electrical activity that leads to chronic epileptic seizures. The concept of “mechanism of epilepsies” refers to any biological

characteristic of the brain that drives or supports recurrent and unprovoked crises.

Epileptogenesis is a dynamic process, in which the genetic and structural alterations in the brain lead to a cascade of molecular and cellular changes, which are associated with the appearance of spontaneous epileptic seizures, such as changes in neurogenesis, neurodegeneration, gliosis, dendritic plasticity, axonal damage, damage to the blood-brain barrier, inflow of inflammatory cells to the brain tissue, reorganization of the extracellular matrix, and reorganization of neuronal activity. Glial abnormalities, including glial scars, various gliomas, and microglia and chronically activated astrocytes, can lead to epileptogenesis due to increased neuronal excitability and inflammatory processes.

The process of epileptogenesis can be divided into three phases²⁶. The first is associated with the occurrence of injury or event, the second latent phase leads to the appearance of abnormal epileptic brain activity, and in the third phase occurs spontaneous epileptic seizures. The factors that have the most important role in the molecular basis of epileptogenesis are as follows: the brain-derived neurotrophic factor-tropomyosin-related kinase B (TrkB, also known as NTRK2) signaling, the mammalian target of rapamycin (mTOR), the repressor element 1 (RE1), and Silencing Transcription Factor, also known as Neuron-Restrictive Silencer Factor.

The imbalance between excitatory and inhibitory neurotransmitters explains the induction of epileptic seizures. GABA A controls the entry of chloride into the cell, and GABA B increases the potassium conductance, decreases calcium entry, and inhibits the pre-synaptic release of other transmitters. The concepts of tripartite neuron explain the pathophysiology of epilepsy, with relevance in the anomalies in the GABAergic function in genetic and acquired animal models of epilepsy, reductions or inhibition mediated by GABA, activity of glutamate decarboxylase, and binding to GABA A sites, this has been reported in studies of human epileptic brain tissue. Abnormalities of GABAergic function, including synthesis, synaptic release, composition, and metabolism of the receptor, lead to a hyperexcitable epileptic state.

Relationship between epilepsy and autism

Sundelin et al. have documented a greater frequency of epileptic seizures in ASD. The frequency range varies from 7% to 42%, currently an association of one third of children with ASD is considered to develop epilepsy²⁷. In our series, we found a prevalence of 30% of children with ASD and Epilepsy²⁸. There is a bimodal

distribution of onset of crisis in patients with ASD and epilepsy: one in the early childhood (before 5 years old) and the other in adolescence after 10 years old²⁹.

The variability in the prevalence of epileptic seizures would probably be due to three factors: (1) the age groups studied, finding a higher percentage of epileptic seizures in studies that include adolescents and young adults, (2) the most severe cognitive disability is related with a higher percentage of epileptic seizures, and (3) the type and degree of language dysfunction, with the highest percentage of epileptic seizures occurring in individuals with verbal auditory agnosia.

All types of seizures can be associated with autism. Keller et al. (2017)³⁰ report partial seizures, atypical absences, myoclonic, and tonic-clonic seizures as the most prevalent, while Tuchman and Rapin (2002)²⁹ show tonic-clonic seizures and atypical absences, in genetic cases as the most common. Matson and Neal (2009)³¹ found a relationship between autistic regression in patients diagnosed with Epilepsy and ASD. Spurling and Tuchman (2015)³² comments that there is no evidence to suggest that epilepsy is the cause of autistic regression; however, it recommends the importance of detecting other deficits, such as language, cognitive, behavioral, and not only to treat seizures. It suggests that there are multiple variables that can guide clinical management where epilepsy, autism, and regression overlap, such as the type of regression, age of onset of crisis, epileptic form activity and the location, orientation, and amount of epileptic form activity.

In studies of multiple models of epilepsy suggest that the balance between the excitatory and inhibitory networks are interrupted, and that the composition and excitatory synaptic efficacy are enhanced, directly, or indirectly. A important excitatory synapses regulator is the glutamate receptor, which is also critical for learning and memory. Therefore, dysregulation induced by an epileptic seizure of glutamate receptor function itself, or that of a “upstream and downstream” mediator can have important effects on learning and cognition.

Ictal activity may provide greater excitability to disrupt synaptic homeostasis, even a brief ictal activity may impair learning, possibly the most sensitive period for seizures that affect cognitive function is during brain development. At that time, the mechanisms of synaptic plasticity are maximum, and excitatory mechanisms predominate on inhibitory. Since the cascades involved in learning and memory are mostly dependent on the activity of neural networks, there is a possibility that this excessive neuronal activity has unexpected effects on normal synaptic function. On the other hand, synaptogenesis is maximal in the

developing brain, and it seems to share many of the same mechanisms with those of synaptic plasticity.

The preschool and grade school ages present high incidences of epilepsy, and this is also the period, in which autism manifests itself. This age window is the natural “critical period,” where synaptic plasticity and synaptogenesis are at the highest level of life. In addition, both epilepsy and autism are partly due to a consequence of a dysregulated synaptic development. When epilepsy and autism co-occur, it is assumed that they may have been the result of a primary interruption of synaptic function due to injury or genetic mutation³⁰. What is not known is whether epileptic activity, which could further disrupt synaptic function, may contribute to the secondary symptomatology of autism.

Glutamate plays a role during the development of the brain by regulating multiple processes, (neurogenesis, neuronal growth, survival of neurons, and synaptogenesis). It is important in the acquisition of emotional behavior. NMDA glutamate receptors are responsible for long-term potentiation, learning, and memory, which altered processes in subjects with autism. In addition, the imbalance between GABA/glutamate can cause epileptic disorders in autism. Genetic studies have found positive associations between autism and a series of polymorphisms in glutamate receptors and transporters, including the mitochondrial glutamate-aspartate transporter (SLC25A12) and the glutamate ionotropic receptor kainate type subunit 2¹⁷.

Mutations in GABA A receptor subunits or mutations in non-GABA A receptor subunit genes that alter GABAergic neuronal activity are associated primarily with epilepsy, but also with autism or both. Genetic mutations other than GABA A receptor subunits, such as tuberous sclerosis, Fragile X Syndrome (FXS) Rett Syndrome, show altered GABAergic signaling. Studies of animal models indicate that the loss of SCN1A function causes significant reductions of sodium in inhibitory GABAergic neurons, suggesting GABAergic circuits that would explain the presence of epileptic seizures in these entities.

The altered expression of GAD 65 and 67 in the GABAergic system has been associated with epilepsy, schizophrenia, ischemia, and traumatic brain injury. In Autism, the level of GAD protein isoforms is reduced (Fatemi et al., 2012)¹⁷. Studies of MRI and neuropathology suggest that the altered proliferation and migration of neuroblasts, the cortical organization, and the development of projection neurons and GABAergic interneurons within the focal brain regions, forming common abnormal neuronal circuits, that would explain the phenotypic manifestations in autism and epilepsy.

Giannotti et al. (2008)³³ reported that epilepsy and epileptiform abnormalities in the EEG were more frequent in children with regression (with loss of neurocognitive abilities in expressive, semantic and pragmatic language, communicative intention, working memory, executive functions, playful abilities, and socialization).

Due to the wide range of age and phenotypes of the ASD group, no single EEG biomarker has been identified that consistently distinguishes individuals with ASD from those without ASD. Wang et al. (2013)³⁴ identified a possible “U” grafoelement within the EEG alterations, with the excess voltage viewed at the theta and gamma frequencies and reduced voltage at medium frequency bands compared to individuals with normal development. The authors speculated that it could result from an abnormal GABAergic tone in inhibitory circuits.

The EEG can also report the neurophysiological mechanisms of the disease in genetic variants of high risk. In duplications of chromosome 15q11.2-q13.1, a subgroup of children exhibits a classic EEG pattern of excessive beta-frequency activity, this characteristic probably reflects the up-regulation of several GABA receptor genes located in the duplicated region. Studies are underway to better characterize this excessive beta-activity, investigate, whether it is characteristic of the EEG, relate to or predict clinical outcomes, particularly the development of epilepsy or ASD.

In addition, they want to find a relationship between specific patterns of EEG with essential deficits or individual behaviors within the ASD, to facilitate clinical stratification³².

Patterns, even controversial, that could distinguish infants with high and low risk of ASD have been identified. The studies have quantified the differences in the trajectories of EEG development, particularly in the gamma band, which reflects the union of neural information from different networks. Other studies have identified an atypical pattern of hemispheric organization based on the asymmetry of the alpha range as well as less functional connectivity between the frontal and parietal regions, in high-risk children compared to low-risk children, independent of the diagnosis of ASD³².

Epileptic syndromes and autism³⁵

Children with ASD who have epilepsy may have epileptic seizures that do not meet the criteria for specific electroclinical syndromes. However, several specific syndromes of epilepsy seem to be risk factors for the subsequent diagnosis of ASD. These are described below.

Aircadi Goutieres syndrome (SAG)³⁶

Rare autoimmune genetic disorder affects the brain and skin. Manifestations may present in utero or post-natal in childhood, characterized by subacute encephalopathy and loss of acquired skills. Severe neurological dysfunction arises as progressive microcephaly, spasticity, dystonia, and cognitive impairment. Associated symptoms include epileptic seizures and glaucoma. Most patients have abnormalities in neuroimaging, including white matter abnormalities and cerebral calcifications, mainly in the basal ganglia.

There are seven known genetic subtypes, caused by mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, or IFIH1; each gene is involved in the intracellular metabolism of normal RNA/DNA. Mutations of TREX1, RNASEH2 A/B/C, SAMHD1, ADAR1, and IFI are associated with developmental delay, regression, and epileptic seizures³⁷.

Infantile spasms

The prevalence of ASD in children with a history of infantile spasms is not consistent, but an association between both is clearer in the tuberous sclerosis complex (TSC1 and 2) and duplications of FOXP1:

In TSC1 and TSC2, hamartina and tuberina, join, and form, a protein complex involved in the regulation of mTOR. The loss of function of the TSC results in the absence of normal inhibition of mTOR, with an increase in Rheb activity and subsequent hyperactivity in mTOR, which leads to disinhibition of protein synthesis and cell growth. The neurological manifestations of TSC include epilepsy, intellectual disability and ASD, as well as specific cerebral malformations and cortical tubules, nodules and subependymal giant cell astrocytomas. Epilepsy occurs in more than 80-90% of patients with TSC. Infantile spasms occur in approximately 20-38% of patients with TSC and are associated with a worse prognosis. ASD is found in 20-60% of individuals with TSC and is equally common in men and women in this population³⁵.

Children with duplications of FOXP1 on chromosome 14q12 have long-term developmental abnormalities that include autistic features. FOXP1 is a specific transcriptional repressor protein that regulates the dorsal-ventral pattern and neurogenesis; its overexpression in the developing anterior brain is associated with thickening of the neuroepithelium, and the evidence supports a role inline change in neuroprogenitor cells. However, the mechanisms that lead to epilepsy and associated

developmental disorders due to changes in the number of copies of this gene are not known³⁸.

Landau–Kleffner syndrome/continuous spike and wave during slow wave sleep (CSWS). The Landau–Kleffner syndrome is an epilepsy-aphasia syndrome of unknown etiology characterized by language regression and continuous spike-wave during slow wave sleep on the EEG. Some children with severe language apraxia have autistic characteristics with a predominance of severe deficit of receptive language. Studies have detected: (1) copy number variants (CNVs) in exogenous deletions of NRXN1, HDAC4, SYNGAP1, ARID1B, SHANK2, CHD2, SHANK3, PTCHD1 intragenic duplication of NRXN1, IL-1RAPL1, and DMD exonic duplication of DMD, duplication partial of DMD, *de novo* CNV, (2) chromosomal abnormalities: unbalanced translocation, 1q duplication syndrome, ring chromosome 8, Down syndrome, and XYY syndrome, (3) genomic disorders with recurrent breakpoints: deletion syndromes 1q21.1, 10q11.21-q11.23, 15q13.3, 16p11.2, 16p13.11, 22q11 (DiGeorge syndrome), 7q11.23 (Williams Syndrome), 17p11.2 (Smith Magenis syndrome) duplication syndromes 1q21.1, 15q11-q13, 16p11.2, 17q12, and 22q11. Xq28 duplication including GDI1 4, 15q25 distal deletion syndrome, and (4) genomic disorders with non-recurrent breakpoints: 9p terminal deletion, 9q34.3 deletion (Kleefstra syndrome), Jacobson syndrome (11q deletion), Mc Dermid Phelan syndrome (22q13 deletion), and GRIN2A mutations in patients with phenotypes of epilepsy-aphasia.

ASD and epilepsy in genetic syndromes³⁴

Several genetic mutations are related to the development of ASD and/or epilepsy and exert their influence on various aspects of neuronal function, not only limiting ion channels and synaptic physiology. These mutations affect proteins involved in all phases of neuronal excitability: anchoring of the synaptic complex, management of the release of synaptic vesicles, control of subcellular signaling pathways, regulation of neuronal migration, and organization of network connections³⁰. Conditions caused by variation in the number of genomic copies or mutations in single genes have been associated with ASD and epilepsy.

Genomic disorders

TRISOMY 21 (DOWN SYNDROME [SD])

5-9% of individuals with DS comply the criteria for ASD. The diagnosis of ASD in this group is a challenge.

The prevalence of epilepsy in patients with DS is 8-13%³⁹. Children with DS and ASD tend to have a general decrease in brain function, and an increased risk of epileptic seizures.

15q11-q13 Duplication Syndrome inherited from the mother. It is the most frequent chromosomal alteration reported in patients with ASD (0.5-3%).

There would be a deregulation of inhibitory synapses, genes that encode the GABA receptor subunits (GABRA5, GABRB3, and GABRG3) in the duplicated 15q11q13 region, which explains the pathogenesis of epilepsy and ASD phenotypes.

CNVs

Some pathogenic CNVs are associated with ASD and epilepsy. 15q11.2 and 16p11.2 deletions and 16p13.11 duplication have been detected with high frequency in individuals with ASD. A possible mechanism of ASD/epilepsy associated with these CNVs is a second mutation in the non-suppressed allele.

Phelan-McDermid syndrome/SHANK3 deletion

The 22q13.3 deletion containing the SHANK3 gene has been associated with early hypotonia, developmental and speech delay, autistic features, lymphedema, and dysmorphisms. The prevalence of epilepsy in these patients is unknown. SHANK3 encodes scaffold proteins found in the postsynaptic space, which regulates the expression of the metabotropic glutamate receptor 5 (mGluR5), regulates the recycling of AMPA receptors and long-term synaptic potentiation, and interacts with the voltage-gated potassium channels Kvβ2 in postsynaptic space. Mice deficient in SHANK3 show autistic behavior and have anomalies in the synapses of the striatum and corticostriatal circuits. Deletions of SHANK1 and mutations in SHANK2 have also been reported in patients with ASD⁴⁰.

Single gene disorders

FXS

It is considered the main monogenic disorder associated with ASD. Occurs when the expansion of a triplet repeat (CGG) leads to the inactivation of the FMR1 gene, resulting in the loss of expression of FMRP (RNA-binding protein, located in the dendritic ribosomes), plays a role in the remodeling synaptic, necessary for normal learning and memory.

The cognitive profile includes hyperactivity, anxiety, tactile defensiveness, gaze avoidance, and socialization difficulties. Epilepsy is reported in 10-20% of individuals. The crisis patterns resemble Benign focal Rolandic epilepsy and typical central-temporal spikes can be observed in up to 60% of patients with FXS with seizures and in 23% of patients without clinical crisis⁴¹. It has been proposed that an ionic current controlled by voltage participate in epileptogenesis by the activation of the mGluR5 receptor. The activation of mGluR5 across multiple synapses in the context of poor FMRP translation control leads to greater electrical excitability.

Mutations in PTEN⁴²

PTEN is a double specificity phosphatase and a tumor suppressor gene, it affects the blocking of the G1 cell cycle and inhibits the PI3K/AKT/mTOR pathway. Macrocephaly and ASD have been reported in children with germline PTEN mutations.

Seizures have been reported in patients with PTEN mutations, including a number with focal cortical dysplasia. Epilepsy seems to be a part of the phenotype for many of the megalencephaly disorders associated with deregulation of the PI3K-AKT-mTOR pathway, but the exact role of mutations in specific genes in this pathway related to seizures and ASD should be clarified.

Disorder related to MECP2 (Rett syndrome)

It predominantly affects women, characterized by intellectual disability, postnatal microcephaly, loss of expressive language, stereotyped movements in hands, and autistic features. The onset of symptoms and regression occur at 6 to 18 months of age after a period of apparently normal development. MECP2 is a transcriptional activator during brain development. Mutations result in "downregulation" of many target genes, loss of MECP2 function reduces GABAergic transmission, and alteration of the glutamatergic unit in specific populations of inhibitory interneurons.

50-90% have epileptic seizures. The type of crisis is variable, the age of onset is rare before 2 years, and the severity of the seizures seems to decrease after adolescence. Mutations specific for MECP2 (p.T158M and p.R106W) were more highly associated with epilepsy.

Disorder related to CDKL5⁴³

X-linked disorder, characterized by early onset of epilepsy, with infantile spasms, and severe neurodevelopmental

delay with postnatal microcephaly, absence of expressive language, and stereotypies of hands. Girls share some characteristics of ASD. The inability to concomitant development and the phenotype of epilepsy are greater than those typically seen in children with classic forms of ASD. The role of the protein CDKL5 (serine-threonine kinase) has to do with the development of dendritic microcolumns, macrocolumns, and adhesion molecules involved in the stabilization of the post-synaptic membrane.

Disorder related to MEF2C

There are mutations with loss of function and deletions of MEF2C on chromosome 5q14.3, characterized by severe intellectual disability, epilepsy, stereotyped movements, and features of ASD.

In most, the cephalic perimeter and brain morphology are normal. The percentage of epilepsy is variable, 20% present infantile spasms, 33% childhood myoclonic epilepsy, 24% generalized epilepsy in childhood, and 23% without epilepsy.

MEFC2 plays several roles during brain development, and is a marker of cortical lamination driven by Tbr1. MEFC2 recognizes a binding site of the synaptic activity response element, which activates a series of genes for synaptic development, dorsal glutamatergic, and ventral GABAergic.

Disorders related to SCN2A

SCN2A encodes the sodium channel voltage dependent Na^(v) 1.2 predominantly expressed in excitatory neurons, the mechanism by which there is loss of function of this channel with secondary hyperexcitability is unclear. The deletion of chromosome 2q24.3 containing SCN2A was reported for the first time in a child with autistic characteristics and intellectual disability⁴⁴. At the same time, several children were identified with a spectrum of severe epilepsies of the early life including Ohtahara syndrome, malignant migratory partial seizures of childhood, and infantile spasms with mutations in SCN2A. In other children, benign neonatal-infantile epilepsy and generalized epilepsy with febrile seizures plus have been reported.

Conclusion

The underlying neurobiological mechanisms for ASD and epilepsy allow us to frequently find both associated pathologies.

This perspective finds support in new genetic mutations discovered for autism and epilepsy that highlight the presence of anomalies in the formation of synapses and the functions that entail an imbalance between excitation and neuronal inhibition.

Every time we diagnose a child on the autistic spectrum, we should consider the possibility of having an epilepsy. It is recommended that patients with diagnosis of epilepsy undergo a neuropsychological evaluation that includes neurocognitive aspects, social, and behavioral skills and interpersonal relationships. The early detection of the association of both pathologies will allow us to provide a better treatment for children and adolescents. It is recommended to perform a directed search and clinical follow-up of this population considering an electroencephalographic follow-up and early intervention in case of diagnosis of epilepsy.

Funding

No financing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

- Zalaquett D, Schönstedt M, Angeli M, Herrera C, Moyano C. Fundamentos de la intervención temprana en niños con trastornos del espectro autista. *Rev Chil Pediatr.* 2015;86:126-31.
- Giovanardi Rossi P, Posar A, Parmeggiani A. Epilepsy in adolescents and young adults with autistic disorder. *Brain Dev.* 2000;22:102-6.
- Besag FM. Current controversies in the relationships between autism and epilepsy. *Epilepsy Behav.* 2015;47:143-6.
- Quijada C. Espectro autista. *Rev Chil Pediatr.* 2008;79:86-91.
- Fombonne E, Marcin C, Manero AC, Bruno R, Diaz C, Villalobos M, et al. Prevalence of autism spectrum disorders in Guanajuato, Mexico: the Leon survey. *J Autism Dev Disord.* 2016;46:1669-85.
- de Práctica Clínica G. Detección y Diagnóstico Oportuno de los Trastornos del Espectro Autista. Chile: Ministerio de Salud de Chile; 2011. p. 12-3.
- David P, Borgeaud K, Bernaschina M. Manifestaciones electroencefalográficas de epilepsia en agrupación de niños con espectro autista. *Rev Chil Salud Pública.* 2007;11:23-7.
- Zablotsky B, Black L. Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 national health interview survey. *Natl Health Statist Rep.* 2015;13:1-20.
- Adam M, Keller TA, Malave VL, Kana RK, Varma S. Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. *Neurosci Biobehav Rev.* 2012;36:1292-313.
- Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Curr Opin Neurobiol.* 2007;17:103-11.
- Kandel E, Schwartz J, Jessell T, Siegelbaum S, Hudspeth J. Principles of Neural Science. 5th ed. New York: McGraw-Hill; 2000.
- Lewis JD, Elman JL. Growth-related neural reorganization and the autism phenotype: a test of the hypothesis that altered brain growth leads to altered connectivity. *Dev Sci.* 2008;11:135-55.
- Herbert M, Ziegler D, Makris N, Bakardjiev A, Hodgson J, Adrien K, et al. Larger brain and white matter volumes in children with developmental language disorder. *Dev Sci.* 2003;6:11-22.
- Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol.* 2005;57:67-81.
- García-Peñas J, Domínguez-Carral J, Pereira-Bezanilla E. Alteraciones de la sinaptogénesis en el autismo. Implicaciones etiopatogénicas y terapéuticas. *Rev Neurol.* 2012;54:41-50.
- Suda S, Iwata K, Shimamura C, Kameno Y, Anitha A, Thanseem I, et al. Decreased expression of axon-guidance receptors in the anterior cingulate cortex in autism. *Mol Autism.* 2011;2:14.
- Fatemi S, Aldinger K, Bauman M, Blaha C, Blatt J. Consensus paper: pathological role of the cerebellum in autism. *Cerebellum.* 2012;11:777-807.
- Fatemi SH, Reutiman TJ, Folsom TD, Rooney RJ, Patel DH, Thurans PD. mRNA and protein levels for GABAA α 4, α 5, β 1 and GABABR1 receptors are altered in brains from subjects with autism. *J Autism Dev Disord.* 2010;40:743-50.
- Kelemenova S, Schmidtova E, Ficek A, Celec P, Kubranska A, Ostatnikova D. Polymorphisms of candidate genes in Slovak autistic patients. *Psychiatr Genet.* 2010;20:137-9.
- Fisher R, Acevedo C, Arzimanoglou A, Bogacz A, Cross H, Elger C, et al. A practical clinical definition of epilepsy. *Epilepsia.* 2014;55:475-82.
- Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia.* 2017;58:522-30.
- Bell GS, Neligan A, Sander JW. An unknown quantity-the worldwide prevalence of epilepsy. *Epilepsia.* 2014;55:958-62.
- Ngugi AK, Bottomley C, Kleinschmidt I, Wagner RG, Kakooza-Mwesige A, Ae-Ngibise K, et al. Prevalence of active convulsive epilepsy in Sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. *Lancet Neurol.* 2013;12:253-63.
- Available from: <http://www.epilepsiamexico.gob.mx>
- Lavados J, Germain L, Morales A, Campero M, Lavados P. A descriptive study of epilepsy in the district of El Salvador, Chile, 1984-1988. *Acta Neurol Scand.* 1992;85:249-56.
- Waszczuk A. Advances in Epileptogenesis-review of the Literature. *Ontario: Health and Wellness;* 2015. p. 295-305.
- Sundelin HE, Larsson H, Lichtenstein P, Almqvist C, Hultman CM, Tomson T, et al. Autism and epilepsy: a population-based nationwide cohort study. *Neurology.* 2016;87:192-7.
- Carvajal M, Torres A, Nuñez P, Granado D. Importancia de realizar un EEG en niñas y niños con TEA y su relación con Epilepsia. *Revista Chilena de Epilepsia.* 2018;8(1):19-25.
- Tuchman R, Rapin I. Epilepsy in autism. *Lancet Neurol.* 2002;1:352-8.
- Keller R, Basta R, Salerno L, Elia M. Autism, epilepsy, and synaptopathies: a not rare association. *Neurol Sci.* 2017;38:1353-61.
- Matson J, Neal D. Seizures and epilepsy and their relationship to autism spectrum disorders. *Neurosci Biobehav Rev.* 2009;33:999-1005.
- Jeste SS, Tuchman R. Autism spectrum disorder and epilepsy: two sides of the same coin? *J Child Neurol.* 2015;30:1963-71.
- Giannotti F, Cortesi F, Cerquiglini A, Miraglia D, Vagnoni C, Sebastiani T, et al. An investigation of sleep characteristics, EEG abnormalities and epilepsy in developmentally regressed and non-regressed children with autism. *J Autism Dev Disord.* 2008;38:1888-97.
- Wang J, Barstein J, Ethridge LE, Mosconi MW, Takarae Y, Sweeney JA. Resting state EEG abnormalities in autism spectrum disorders. *J Neurodev Disord.* 2013;5:24.
- Lee BH, Smith T, Paciorkowski AR. Autism spectrum disorder and epilepsy: disorders with a shared biology. *Epilepsy Behav.* 2015;47:191-201.
- Svingen L, Goheen M, Godfrey R, Wahl C, Baker E, Gahl W, et al. Late diagnosis and atypical brain imaging of Aicardi-Goutières syndrome: are we failing to diagnose Aicardi-Goutières syndrome-2? *Dev Med Child Neurol.* 2017;56:1307-11.
- Livingston JH, Crow YJ. Neurologic phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, and IFIH1: Aicardi-Goutières syndrome and beyond. *Neuropediatrics.* 2016;47:355-60.
- Seltzer LE, Ma M, Ahmed S, Bertrand M, Dobyms WB, Wheless J, et al. Epilepsy and outcome in FOXP1-related disorders. *Epilepsia.* 2014;55:1292-300.
- Rasmussen P, Börjesson O, Wentz E, Gillberg C. Autistic disorders in down syndrome: background factors and clinical correlates. *Dev Med Child Neurol.* 2001;43:750-4.
- Sarasua SM, Boccuto L, Sharp JL, Dwivedi A, Chen CF, Rollins JD, et al. Clinical and genomic evaluation of 201 patients with Phelan-McDermid syndrome. *Hum Genet.* 2014;133:847-59.
- Berry-Kravis E. Epilepsy in fragile X syndrome. *Dev Med Child Neurol.* 2002;44:724-8.
- Sunnen CN, Brewster AL, Lugo JN, Vanegas F, Turcios E, Mukhi S, et al. Inhibition of the mammalian target of rapamycin blocks epilepsy progression in NS-Pten conditional knockout mice. *Epilepsia.* 2011;52:2065-75.
- Zhu YC, Li D, Wang L, Lu B, Zheng J, Zhao SL, et al. Palmitoylation-dependent CDKL5-PSD-95 interaction regulates synaptic targeting of CDKL5 and dendritic spine development. *Proc Natl Acad Sci U S A.* 2013;110:9118-23.
- Berry-Kravis E, Raspa M, Loggin-Hester L, Bishop E, Holiday D, Bailey DB. Seizures in fragile X syndrome: characteristics and comorbid diagnoses. *Am J Intellect Dev Disabil.* 2010;115:461-72.