PRE, PERI AND POSTNATAL RISK FACTORS ASSOCIATED WITH PERVASIVE DEVELOPMENTAL DISORDERS

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Abstract: *Risk factors represent a research priority regarding the cause of autism spectrum disorders (ASD). We pursued the characterization of a series of environmental factors suspected as being risk factors, involved in the etiopathogenesis of ASD. We conducted a clinical trial, case control, analytical, observational, and retrospective. We included in the study 54 children diagnosed with ASD and 54 healthy children. For inventorying the risk factors, we used a set of questions about the pre/ peri and postnatal periods. We performed statistical analysis for assessing the existing link between the disease and the risk factor.We observed a statistically significant relationship between ASD group and the exposure to pollutants during pregnancy, infections in the newborn period and parent's ages. In addition to case control type small studies, a cohort type approach is required in order to distinguish different genetic and environmental factors involved in the pathogenesis of ASD.*

Cuvinte cheie: *autism, factori de risc, copii □i adolescen□i*

Rezumat: *Factorii de risc reprezintă o prioritate a cercetărilor privind cauza tulburarilor de spectru autist (TSA). Obiective. Caracterizarea unei serii de factori de mediu, suspecta□i ca fiind factori de risc, implicati în etiopatogenia TSA. Metoda. Am realizat designul unui studiu clinic, caz control, analitic, observa□ional, retrospectiv. Am inclus in studiu 54 de copii cu diagnostic de TSA □i 54 de copii sănăto□i. Pentru inventarierea factorilor de risc am folosit un set de întrebări legate de perioada pre/peri □i postnatală. Am efectuat prelucrări statistice pentru evaluarea existen□ei unei legaturi între boală □i factorul de risc. Rezultate. Am observat o rela□ie semnificativă statistic între lotul TSA □i expunerea la poluan□i pe perioada sarcinii, înfecţiile din perioada de nou-născut si varsta parintilor. Concluzii. Pe lângă studiile mici, tip caz martor, este necesară o abordare tip cohotă pentru a distinge diferi□i factori genetici □i de mediu implicati in patogeneza TSA.*

INTRODUCTION

Risk factors represent a research priority regarding the cause of ASD. It is necessary to establish their exact specification, especially the interaction of environmental and genetics factors in the most vulnerable periods of development such as pregnancy and neonatal period. Small focused studies are necessary to test hypotheses and to create the opportunity for greater replicated studies. As the studies for relatively rare medical conditions, case control studies may be a necessary first line. Some environmental factors, associated in current studies with an increased risk for developing autism spectrum disorders, have a higher discriminative power.

OBJECTIVES

We pursued the characterization of a series of environmental factors suspected as being risk factors, with a high probability of involvement in the etiopathogenesis of the autistic spectrum disorders. Main objective: to identify possible risk factors associated with the development of ASD (environmental factors, common and individual associated with pre, peri and postnatal periods). Secondary objectives: when identifying risk factors, to do the analysis of their discriminative value between ASD group and control group, determine a discrimination optimal threshold value (cut-off point) and compare the discriminative value of two or more risk factors.

MATERIAL AND METHOD

We conducted a clinical trial, case control, analytical, observational, retrospective, directed at a well-defined category of patients: children with autistic spectrum disorder.

Participants. We've put together a group of 54 children diagnosed with ASD and a group of 54 healthy children.

Inclusion criteria for the study were: boy or girl aged 1 to 13 years (inclusive); ASD diagnosis according to the international diagnostic criteria of DSM IV TR and ICD-10 set after structured clinical interview for infant, child and adolescent disorders (KID-SCID); caregivers agreement to participate in the study, after being explained and understood the purpose of the study and clinical protocol.

Exclusion criteria were: children with a known medical condition (metabolic, genetic, neurological or major somatic diseases), children aged over 13 years, children with incomplete medical records, adopted children or being in foster care.

Instruments. For the diagnostic procedure we used the clinical interview for infant, child and adolescent disorders (KID-SCID). For inventorying the risk factors, we used a set of questions about the pre/ peri and postnatal periods that were addressed to the caregivers. These questions were focused on common and individual environmental factors.

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Procedure. For all patients who met the inclusion and exclusion criteria in the study we conducted a psychiatric and somatic evaluation. All participants in the clinical group satisfied the DSM-IV TR and ICD-10 international diagnosis criteria for an ASD. Caregivers were asked to respond as accurate as they could to the set of questions about the pre / peri and postnatal periods of their child.

Data analysis. The data were entered into an SPSS database. For data analysis we used SPSS statistical package (version 17) and MEDCALC program. We performed statistical processing for the assessment of a existing link between the disease and the risk factor and to quantify the importance of this link. Initially we made a simple descriptive statistic comparison of the data between ASD and the control groups. Subsequently, we divided the analyzed risk factors in two categories:

1. Nonparametric risk factors (measured on categorical scales) and
2. Parametric risk factors (measured on interval scales or reports).

The relationship between each category of factors with ASD was tested through specific procedures for the two types of scales. The analysis procedure used to asses the nonparametric factors in relation to the ASD group consist in using the bivariate distribution of the subjects in contingency tables such as risk factor (categories) X disease (control versus ASD). Each distribution was also accompanied by the value of hi square test of association (χ^2) and the analysis of this value statistical significance. Since hi square values do not vary in the same range as the parametric correlation coefficients (between -1 and 1), at χ^2 values we also added the nonparametric correlation coefficient (φ) calculated as the square root of the ratio between χ^2 and the sample size (N) on which the analysis was done. Regarding the parametric risk factors, for testing their relationship with the affiliation in one of the two groups included in the analysis, we used the t test with independent samples. To study the discriminative value of a risk factor between ASD and control groups, we used the ROC (Receiver Operating Characteristic) curves analysis described for each of the two variables.

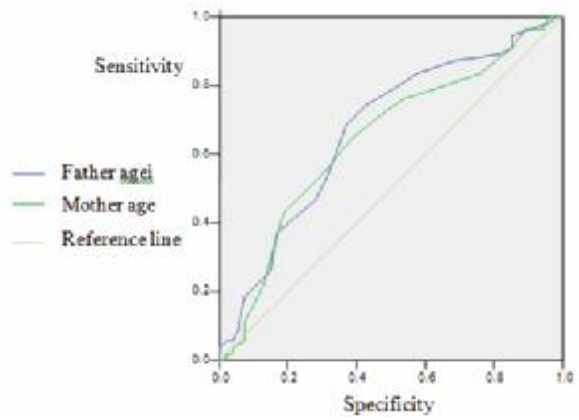
RESULTS AND DISCUSSIONS

Between ASD and control groups there was a balanced distribution with regard to gender ($\chi^2 = 0.52$ $p > 0.05$, $\varphi = 0.02$ $p > 0.05$); origin environment ($\chi^2 = 0.20$ $p > 0.05$ $\varphi = -0.04$ $p > 0.05$); level of parents education ($\chi^2 = 0.54$ $p > 0.05$, $\varphi = 0.07$ $p > 0.05$); drugs consumption during pregnancy ($\chi^2 = 0.98$ $p > 0.05$, $\varphi = 0.09$ $p > 0.05$); alcohol consumption during pregnancy ($\chi^2 = 3.08$ $p > 0.05$ respectively $\varphi = 0.16$ $p > 0.05$); smoking during pregnancy ($\chi^2 = 0.21$ $p > 0.05$ respectively $\varphi = -0.04$ $p > 0.05$); caesarean section ($\chi^2 = 0.07$ $p > 0.05$ and $\varphi = -0.02$ $p > 0.05$). The familial histories of different psychiatric disorders were not balanced distributed and their association with ASD group was of borderline statistical significance ($\chi^2 = 3.53$ $p = 0.06$, $\varphi = -0.18$, $p = 0.06$). We observed a statistically significant relationship between ASD group and the exposure to pollutants during pregnancy (pesticides, volatile solvents, heavy metals) ($\chi^2 = 6.27$ $p < 0.05$, $\varphi = -0.24$ $p < 0.05$), with an average size of the statistical effect for this risk factor. From the 42 subjects with hypoxia at birth, 29 belong to the ASD group and only 13 to the control group, suggesting a relationship between two variables. This is confirmed by both value of hi square test ($\chi^2 = 9.97$ $p < 0.05$) and non-parametric correlation coefficient fi ($\varphi = -0.30$ $p < 0.05$), both being statistically significant.

With regard to the infections in the newborn period, the data showed that there is an association between this factor and ASD ($\chi^2 = 6.35$ $p < 0.05$ respectively $\varphi = -0.24$ $p < 0.05$). We found no statistically significant differences between ASD and control groups in the duration of pregnancy and birth weight ($t = -0.31$ $p > 0.05$ and $t = -0.32$ $p > 0.05$).

In terms of father age, the results showed a significantly higher mean age for ASD group subjects ($M = 31.00$, $SD = 5.24$) than for the control group subjects ($M = 28.09$, $SD = 4.70$), $t(106) = 3.03$, $p < 0.01$. The statistical effect size in this context, measured using Cohen's d coefficient is $d = 0.58$ which means a medium effect. With regard to the maternal age, the results also showed a significantly higher mean age for ASD group subjects ($M = 28.13$, $SD = 4.77$) than the control group subjects ($M = 25.93$, $SD = 5.10$), $t(106) = 2.31$, $p < 0.05$. The statistical effect size, also measured using Cohen's d coefficient is $d = 0.44$ which means a medium effect. Maternal age discriminate significantly better than a random test, the corresponding area under the ROC curve was 0.64 (from the maximum AUC = 1), statistically significant value ($Z = 2.70$ $p < 0.01$). Father's age discriminate significantly better than a random test, the area under the corresponding ROC curve was 0.66, statistically significant value ($Z = 3.25$ $p < 0.01$). The curves of the two variables have similar evolutions, the described areas under ROC curves by the variables maternal and father age showed lack of difference in the discriminative value. The difference between the areas described by the two curves (0.02) was not a statistically significant one ($Z = 0.48$ $p > 0.05$), which means that there are no differences in their ability to discriminate between ASD and the control groups (fig. no1 insert about here).

Figure no. 1. The ROC curves corresponding to the parent's age



CONCLUSIONS

1. We identified no statistically significant relationships between the factors gender, origin environment, parent's education level, drugs use during pregnancy, alcohol consumption during pregnancy, smoking during pregnancy, caesarean section and ASD group.
2. Association of family history of mental illness with ASD group is borderline statistical significant ($\chi^2 = 3.53$ $p = 0.06$, $\varphi = -0.18$ $p = 0.06$).
3. The mean father's age in the ASD group is significantly higher compared with that of the control subjects ($t(106) = 3.03$, $p < 0.01$). The mean maternal age in ASD group is significantly higher compared with that of the control subjects ($t(106) = 2.31$, $p < 0.05$).
4. Maternal age ($Z = 2.70$ $p < 0.01$) and father's age ($Z = 3.25$ $p < 0.01$) discriminate significantly better than a random test. We detected no differences in the ability of the variables mother and father's age to discriminate between

ASD and the control groups (Z = 0.48 p> 0.05).

5. We observed a statistically significant relationship between ASD group and exposure to pollutants during pregnancy (pesticides, volatile solvents, heavy metals) ($\chi^2 = 6.27$ p <0.05, $\varphi = -0.24$ p <0.05), with an average size of the statistical effect for this risk factor.
6. We found a statistically significant relationship between ASD group and hypoxia at birth factor compared with the control group ($\chi^2 = 9.97$ p <0.05, $\varphi = -0.30$ p <0.05). The size of the statistical effect for this risk factor is an average one. This variable discriminate significantly better between the two groups than a random test (area = 0.64, sensitivity of 0.53 and a specificity of 0.75, p <0.05).
7. Association of neonatal infection, bacterial or viral, which required pharmacotherapy, and ASD group was statistically significant compared with control subjects ($\chi^2 = 6.35$ p <0.05, respectively $\varphi = -0.24$ p <0.05), but this variable did not discriminate better between the two groups than a random test.
8. In addition to case control type small studies, a cohort type approach on large samples is required in order to distinguish different genetic and environmental factors that may explain the pathogenesis of ASD and the comorbidities frequently presented. These studies should aim the development of standard methods to collect and storage the biological samples during pregnancy and neonatal period, clinical monitoring and subjects' exposure to different environmental factors from birth, with concomitant collection of DNA samples. Also, it is important to study the influence of the disorder clinical profile, particularly in ASD subpopulations. These epidemiological studies must be interdisciplinary, made during pregnancy and neonatal period.

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