

To the Chair of the Scientific Jury,  
determined by order of  
The Rector of Medical University  
"Prof. Dr. Paraskev Stoyanov" -  
Varna

## REVIEW

**From prof. Ivan Olegovich Litvinenko, MD**, Department of Pediatrics, Medical University - Sofia, Head of the Pediatric Neurology Clinic at the State Pediatric Hospital "prof. Ivan Mitev" - Sofia

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Appointed as a member of the Scientific Jury by Order No. P-109-81/21.03.2024, pursuant to Article 4, paragraph 2 of the Law on the Development of Academic Staff in the Republic of Bulgaria, and in connection with the procedure for the acquisition of the educational and scientific degree "Doctor" in the doctoral program "Pediatrics", professional field 7.1. Doctor of Medicine, field of higher education 7. In accordance with Protocol No. 1/ 02.04.2024 of the meeting of the Scientific Jury, I present the review prepared by me.

**SUBJECT: The dissertation work of Dr. ZHIVKA EMILOVA CHUPURKOVA, entitled - "QUALITY OF LIFE AND COMORBIDITY IN CHILDREN WITH EPILEPSY", submitted for the award of PhD with scientific supervisors Prof. Dr. Miglena Dimitrova Georgieva, PhD and Prof. Dr. Veneta Sasova Bozhinova - Chamova, PhD. The reviewing of the materials submitted for the competition is based on the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its implementation, as well as the Regulations on the Conditions and Procedure for the Acquisition of Scientific Degrees and the Occupation of AD and Qualitative Criteria for the Development of the Academic Staff of MU "Prof. Dr. Paraskev Stoyanov" - Varna.**

### **Brief biographical data and professional development**

Dr. Zhivka Emilova Chuperkova has completed her higher education with a Master's degree in Medicine in 2013 at the Medical University of Varna. She started her medical practice as a doctor at AIMPP-DAAR "Dr. Silvia Ilieva-Baltieva", Varna. She graduated from the University of Varna in 2013. From 2014 to 2018 she was a specialist in pediatrics at the University Hospital "St. 2014 - 2014-2014. She has been working at the University of St. Marina in Varna since 2014. From 2019 to 2021 she is a specialist in pediatric neurology at the Second Children's Clinic of the same hospital. Since 2018, after a competition, she has been an assistant professor at the Department of Pediatrics at MU - Varna. In 2018 she has a recognized specialty in Pediatrics. In 2021 he acquired the specialty of Pediatric Neurology, and in the same year he acquired a professional qualification

in the highly specialized activity of Clinical EEG. As of 2020, he is a doctoral candidate in Pediatrics.

Dr. Chuperkova is fluent in written and spoken English and German.

**Membership:** 1. 1. Bulgarian Society of Child Neurology, Psychiatry and Developmental Psychology.

### **Research activity**

Dr. Chuperkova has 6 publications and 13 reports at scientific forums and participates in the scientific project "Feel 4 Diabetes" - Medical University - Varna.

**The dissertation of** Dr. Chuperkova is presented in 198 pages, based on 304 literature sources (Medical University "Prof. Dr. Paraskev Stoyanov" - Varna) and is illustrated with 84 figures and 65 tables and 2 annexes. It is structured according to the classical model.

The dissertation is very well designed and addresses a topical problem from both a scientific and practical point of view. Epilepsy has a wide palette of manifestation from benign, self-limiting forms to those with marked treatment refractoriness, from idiopathic, often with genetic predisposition to symptomatic within an underlying disease, which in itself can give an impact on quality of life. Quality of life reflects different aspects of life - medical, social, economic, etc. The term 'health-related quality of life' refers to the impact of disease and its treatment on overall quality of life. Specially developed instruments (questionnaires) are used to study it. There are many such questionnaires available and this can often lead to difficulties in selecting the most appropriate one for a particular purpose. It is accepted as standard that measurement is carried out using data provided by the patient. However, a characteristic feature of the study of children is the need to also collect information from a parent or other person familiar with the case. In order to carry out a reliable survey in this age group, specific instruments are needed to collect data from both the child and the parents, and in the official language of the country in which they are administered. The KINDLR is one of the instruments enabling the assessment of health-related quality of life in children and adolescents. Conducting a specific study on comorbidity in Bulgarian childhood patients with epilepsy and its impact on quality of life expands the knowledge on this topic nationally and allows to identify causal relationships between key demographic, social, medical, etc. indicators and to highlight those with practical relevance for improving the quality of life of children with epilepsy and comorbidities. After a thorough and analytical review of the literature, Dr. Chuperkova provides a brief summary and draws the main conclusions in 6 points and forms 4 working hypotheses, based on which she formulates the aim of the dissertation. To accomplish this goal, 5 tasks were specified: To identify 100 pediatric patients with epilepsy to be included in the study, along with one of their parents; To design a specialized study protocol for the identified cohort; To select a validated methodology for the study of quality of life in children to be applied to the study contingent; To analyze and summarize the data on available comorbidity, classifying them by disease groups; To look for correlations and causal relationships between the studied indicators and quality of life.

<sup>R</sup> **Materials and Methods.** Patients were divided into 3 age groups according to the versions of the questionnaire. The study was approved by the Research Ethics Committee at MU "Prof. Dr. Paraskev Stoyanov" - Varna. All participants (parents) were familiarized with the procedures in advance and signed an informed consent form for their and their child's participation. The surveys were conducted in the bases - children's clinics of the University Hospital "Sveta Marina"- St. Варна, ДКЦ „Света Марина“- гр. Medical Center "Dr. Antonov" Ltd. Petrich, for which permission has been obtained from the Research Ethics Committee (REC) of MU "Prof. Dr. Paraskev Stoyanov" Varna. A variety of statistical methods were used: 3.1. descriptive (descriptive), statistical estimation, hypothesis testing, correlation analysis, linear regression analysis.

**The results are presented** within 65 pages. The data are examined at 14 points. Demographic data are analysed first. Of note, the result of Fisher's test ( $p=0.01$ ) showed a significant association between the presence of comorbidity and the professional field in which the mother works. As expected, a predominance of the field "Other" was reported for mothers of children with comorbidity. In the comorbidity group, there was a prevalence of irregular attendance and non-attendance, as well as lower grades. With regard to the second indicator, pregnancies at birth, the analyses conducted showed no significant differences in birth weight, height and head circumference between the groups with and without comorbidity, and between age groups. The third indicator analysed was Neuropsychiatric development. Again, as expected, there were significant differences between children with and without comorbidity. The fourth indicator is - health status of the child according to the parents. There were significant differences between children with and without comorbidity, with the negative response "rather poor" missing in the group without comorbidity. In relation to the fifth indicator, data on epilepsy, there were significant differences between children with and without comorbidity in terms of the type of seizures observed, with concurrent focal and generalised seizures dominating in the group with comorbidity. Furthermore, In the group with comorbidity, lower age at first seizure was reported. Significant differences by age group were also reported with respect to the number of medications taken. There was a significant prevalence of structural/metabolic epilepsy in patients with comorbidity. Comorbidity analysis follows. For ease of perception, the diverse palette of comorbidities are presented in tabular form. Additional questions in the questionnaire specified how many comorbidities each patient had, whether they were diagnosed before or after the onset of epilepsy, and whether they were being treated and monitored by an appropriate specialist. Comorbidity was recorded in 60 of the patients. The results of laboratory, EEG and imaging tests were presented next. EEG results were abnormal in 73 children and dominated in those with comorbidity. Regarding imaging, it is noted that more abnormal imaging results were found in the comorbidity group. The section - measurements includes information on vital signs measurements (weight, height, head circumference, BMI, BP and HR) as well as neurological status - normal or abnormal. The doctoral student found a higher mean BMI in the comorbidity group. The neurological status of the participants was abnormal in 28 cases and all of them were in the comorbidity group. Next, we review the completion characteristics of the KINDL questionnaire<sup>R</sup>

and then the interview characteristics. There was a significant prevalence of difficulties for the child in the comorbidity group. Section 11 presents the reliability of the English version of the questionnaire. Both children and parents rated the domain "Emotional well-being" highest and "Self-esteem" lowest. Comparison of the mean values for quality of life calculated from children's and parents' responses showed a difference in the indicator "Chronic illness/long hospital stay", on which children rated their quality of life lower. Children without comorbidities rated the "Physical well-being" domain highest, while their parents rated the "Friends" domain highest. Children with comorbidity rated the domain "Emotional well-being" the highest, and their parents rated "Family" the highest. The lowest scores were for 'Self-esteem'. There were no statistically significant differences between the responses of children with comorbidities and their parents, except for "Chronic illness/long hospital stay", on which children rated their quality of life lower. An independent samples t-test reported significantly higher scores on all indicators in the non-comorbidity group, except "School" and "Family". Regarding parents' responses, statistically significantly higher scores were reported for all indicators in the non-comorbidity group except for "Family". The indicators "General quality of life" and "Chronic disease" were compared in the three age groups by univariate analysis of variance. In the Correlation Analysis section, correlations were sought between various indicators for which information was collected through the questionnaire and the overall quality of life calculated for the KINDL questionnaire<sup>R</sup> - child and parent responses, equated to a scale of 1 to 100. Finally, a linear regression analysis was conducted to assess the extent to which indicators identified after the correlation analysis (independent variables) could predict the quality of life score.

**In the discussion section** , which is spread over 22 pages, the results obtained are analysed and compared with the literature data, with explanations and hypotheses being given and the relevant conclusions being drawn organically in the conclusion.

The majority of the responses were rated by the interviewer as somewhat credible, and for 15 of the children's responses as less credible. Difficulties were reported for about half of the children and for 8 of the parents. The significant prevalence of difficulties for the children in the comorbidity group is understandable, as is the strong association in magnitude between the presence of comorbidity and difficulties for the child completing the KINDLR questionnaire. It can be assumed that the characteristics of the interview allow the information obtained to be considered as generally reliable. The biases described are not surprising given the nature of the method applied to the specific study population, but they should not be considered critical to the results obtained.

The reliability of the Bulgarian version of the KINDLR questionnaire was determined in the generally accepted way, both separately for each of the variants - KiddyKINDL, KidKINDL, KiddoKINDL and for the additional module "Epilepsy" in children, and for KiddyKINDL and Kid/KiddoKINDL in parents. As required by the authors, analyses were performed after automated recoding of negative responses and standardization of coding across questions. The high reliability

achieved in all versions and the absence of questions that compromise it are a testimony to the feasibility of the questionnaire and to the quality of the data obtained.

**In conclusion,** the information presented so far, taken as a whole, confirms the working hypotheses of the study. The contingent of the present study is found to possess socio-demographic characteristics that are indicative of relative homogeneity with balanced differences also observed in paediatric practice. The findings suggest that a variety of factors, along with characteristics of the underlying disease, influence the quality of life of children with epilepsy. A marked deterioration in quality of life was reported in the presence of comorbidity. The psychiatric and neurological comorbidities are highlighted, emphasizing the need for increased attention, focused examination, neuropsychological follow-up and psychiatric consultation. The nature of the pediatric population suggests consideration of learning problems, which, added to the medical ones, highlight the social dimensions of the problem.

**7 conclusions were drawn.** Of these, I would distinguish conclusion No. 3. The selected and administered KINDLR questionnaire demonstrates high reliability; and No. 1. Higher quality of life, as calculated for KINDLR according to children's responses, is most heavily weighted by the absence of mental co-morbidities (16%), the presence of purposeful play activities (15%), and better momentary health (13%), while according to parents' responses, the leading factors are better health of the child currently (19%) and in general (16%), and higher school performance (10%).

I think the framing of the conclusions could be improved - to be more synthesized and not sound more like results.

**I also accept the outlined contributions** of the present work divided into those of scientific theoretical character - 3 in number and of scientific applied character - also 3.

Of the contributions of scientific and theoretical nature the most important for me are № 1.2.2.

High reliability of all used versions of the quality of life questionnaire KINDLR in Bulgarian language has been established; and № 1.3.3. Statistically significant dependencies of the quality of life of children with epilepsy with and without comorbidity on various socio-demographic and medical factors have been determined;

Among the contributions of scientific and applied nature I highly appreciate № 2.1 1.3. Statistically significant dependencies of the quality of life of children with epilepsy with and without comorbidity on various socio-demographic and medical factors have been determined;

**The results of the thesis are reflected in a total of 4 scientific communications.** Of these, 2 are original articles in scientific medical journals - one in Cyrillic and one in Latin, and 2 are presentations at scientific forums in Bulgaria with printed abstracts in conference proceedings, which meets the requirements for a PhD.

**CONCLUSION:** With her PhD Dr. Zhivka Emilova Chuperkova presents herself as a mature researcher, able to conduct research at a high scientific level and to analyze complex scientific results, to build hypotheses and draw reasonable conclusions.

The scientific values of the present work satisfy the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the internal criteria of MU-Varna for the acquisition of the *educational and scientific degree* "**DOCTOR**" and I take the liberty to recommend to the distinguished members of the Scientific Jury conducting the defense that it be awarded to Dr. Zhivka E. Chupuerkova.

07.05.2024

Reviewer:

Заличено на основание чл. 5,  
§1, б. „В“ от Регламент (ЕС)  
2016/679

/ Prof. Ivan Litvinenko, Ph. /