ABSTRACT

of the doctoral dissertation of Galym Aigerim on the topic «Features of the Development of Demyelinating Diseases of the Multiple Sclerosis Spectrum in Children in the Kazakh Population», submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in specialty 6D110100 – «Medicine»

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Relevance of the Topic

Demyelinating diseases of the central nervous system (CNS), including multiple sclerosis (MS), represent one of the most complex problems in pediatric neurology owing to the steady rise in incidence, early onset and high risk of disability at a young, working age. Current clinical and imaging data show that the latent onset of the pathological process occurs precisely in childhood in 96% of cases. MS increasingly manifests in childhood and adolescence, accounting, according to international data, for up to 5% of the overall pool of diagnosed cases.

In Kazakhstan this pathology represents a serious medical and social problem. Current estimates of the overall prevalence of MS in the country are in the thousands of patients, while the pediatric cohort (under 18 years) forms a stable group numbering, by various estimates, 150–200 verified cases. The distribution of morbidity across the republic is heterogeneous, predominating in the Eastern, Central and Northern regions of Kazakhstan, as well as in major cities. Against the backdrop of a global rise in demyelinating pathology, Kazakhstan has also seen an unfavorable trend in overall mortality, which has more than doubled in recent years. The latent course and insufficient detection of demyelinating diseases in children in Kazakhstan make it necessary to integrate standard clinical, neuroimaging and laboratory criteria with a priority study of the previously unexplored immunogenetic profile (HLA-DR loci) for early verification, prediction of disease course and personalization of therapy in the Kazakh population.

Current diagnostic practice relies mainly on clinical and imaging criteria developed for adults, without accounting for the ethnic features of the immunogenetic profile of the Kazakhstani population, which hampers early diagnosis of juvenile MS. The study was carried out under state research grant AP09562785 (Ministry of Science and Higher Education of the Republic of Kazakhstan), consistent with the priorities of the country's science and technology policy and with the Law of the Republic of Kazakhstan “On Science and Technology Policy”. The novelty of the work lies in the first comprehensive comparison, for the Kazakh population, of the clinical, neuroimaging, serological and HLA-associated characteristics of demyelinating diseases of the multiple sclerosis spectrum in children.

Aim of the Dissertation Research

To optimize early diagnosis on the basis of clinical and immunogenetic features, in order to substantiate timely therapy for demyelinating diseases of the multiple sclerosis spectrum in children.

Research Objectives

1. To analyze the clinical-neurological, neuroimaging and laboratory features of the development of demyelinating diseases belonging to the multiple sclerosis spectrum in children.

2. To study the genetic profile of the DR-region genes of the HLA system in children (DRB1, DQA1, DQB1) and adolescents with demyelinating diseases of the multiple sclerosis spectrum.

3. To determine serological markers of autoimmune demyelination in juvenile forms of multiple sclerosis, in particular autoantibodies to myelin oligodendrocyte glycoprotein (MOG).

4. To assess the medical, social and organizational aspects of care provided to children with demyelinating diseases in the Kazakhstani population.

5. To develop a diagnostic algorithm for multiple sclerosis in children to improve early detection and personalized patient management.

Research Materials and Methods

A case-control clinical and genetic study was conducted (recruitment period 2015–2021) on the basis of the Aksai Clinic of "Asfendiyarov KazNMU" and the Atchabarov Research Institute of Fundamental and Applied Medicine (Almaty). The study was approved by the Local Ethics Committee of KazNMU (protocol No. 12 (123) dated 22.12.2021); written informed parental consent was obtained for all participants. The work was carried out under state research grant AP09562785 (Ministry of Science and Higher Education of the Republic of Kazakhstan).

Object of the study: Patients of the Aksai University Clinic of the Asfendiyarov Kazakh National Medical University.

Study group: 34 children with demyelinating diseases (ages 4-18 years; 24 girls, 10 boys), including acute disseminated encephalomyelitis, juvenile multiple sclerosis, Rasmussen's leukoencephalitis, Schilder's leukoencephalitis, and Devic's neuromyelitis optica (DNMO). Of these, 11 were Kazakh children with MS, 7 with leukoencephalitis (all Kazakhs), and 6 with DNMO (all Kazakhs).

Comparison group: 10 Russian children with multiple sclerosis.

Control group: 15 children with other neurological disorders (ages 5-18 years) – used for genetic comparison.

Research methods:

Clinical and instrumental: assessment of neurological status using the EDSS disability scale; MRI of the brain and spinal cord; optical coherence tomography (OCT) measuring retinal nerve fiber layer (RNFL) thickness.

Immunological: determination of serum antibodies to aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG).

Immunogenetic: genotyping of HLA class II loci (DRB1, DQA1, DQB1) with calculation of allele and haplotype frequencies and relative risk of disease.

Sociological: parental questionnaires; extraction of data from medical records (case histories, outpatient charts).

Statistical analysis: data were processed using descriptive and analytical statistics, including calculation of means and standard deviations, parametric and non-parametric tests (Student's t-test, χ^2), correlation analysis, and calculation of relative risk (RR) with 95% confidence intervals. Statistical significance was set at $p < 0.05$.

Main Research Results

The results reveal several clinically important patterns consistent with international data, while also pointing to problems specific to this context.

Neuroimaging and optical coherence markers.

The MRI pattern of juvenile MS was characterized by round demyelinating lesions with homogeneous T2-hyperintense and T1-hypointense signal, predominantly periventricular in location; disease activity during exacerbation was confirmed by gadolinium contrast

enhancement. An age-related feature was an atypical topographic distribution of plaques involving the cortical and subcortical regions.

Retinal nerve fiber layer (RNFL) atrophy, as a marker of axonal damage, was verified in 95% of patients with NMOSD, 80% with juvenile MS (predominantly the temporal segment, including subclinical optic neuritis), and in only 10–35% of cases in other demyelinating pathologies, confirming the method's high differential-diagnostic value.

Immunogenetic and serological findings.

Immunogenetic analysis: real-time PCR genotyping was performed for the HLA-DRB1 (13 alleles), HLA-DQA1 (8 alleles) and HLA-DQB1 (11 alleles) loci; allele and haplotype frequencies were compared using Fisher's exact test ($p < 0.01$) with calculation of relative risk (RR).

Serological markers: anti-MOG-IgG was verified in 65% of patients with juvenile MS (sensitivity 40.5%, specificity 65%); in the control group, antibody levels remained within reference values (below 10 ng/mL).

Based on the data obtained, a comprehensive personalized algorithm for the early diagnosis of juvenile MS was developed, integrating clinical-serological criteria and specific features of the HLA profile in the Kazakh population to enable timely initiation of targeted therapy.

Scientific Novelty

1. For the first time in Kazakhstan, molecular-genetic typing of the HLA-DRB1, DQA1 and DQB1 loci was performed in children with demyelinating diseases.
2. The features of the distribution of HLA alleles and haplotypes in children with demyelinating diseases were established.
3. For the first time, genetic features of demyelinating diseases, including MS, were identified in children in the Kazakh population.
4. A personalized approach to the diagnosis of MS in children based on HLA typing was developed.
5. For the first time in the Kazakh pediatric population, the diagnostic value of the serological (MOG-IgG) and neuro-ophthalmological (RNFL) markers of subclinical CNS damage was established, forming the basis of a comprehensive diagnostic algorithm.

Key Statements Submitted for Defense

1. In children of the Kazakhstani population with demyelinating CNS diseases, a significant association was established with the HLA-DRB1*15–DQA1*01:02–DQB1*06:02 haplotype, detected in a state of linkage disequilibrium.
2. The specific pattern of distribution of HLA alleles and haplotypes in patients with demyelinating diseases, statistically significantly different from the control group, indicates a genetic predisposition to autoimmune CNS damage.

3. Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) are detected in 65% of children with multiple sclerosis and have diagnostic value (sensitivity 40.5%, specificity 65%), confirming their role as a biomarker.

4. Neuro-ophthalmological changes, including thinning of the retinal nerve fiber layer, are detected in 80% of children with MS and may be present in the absence of clinical manifestations, indicating a subclinical neurodegenerative process.

5. Determination of the DRB1*15~DQA1*01:02~DQB1*06:02 haplotype helps neurologists establish a more accurate diagnosis and select targeted immunomodulatory therapy in a timely manner.

Practical Significance of the Results Obtained

1. The identification of clinical, immunological and genetic markers of the disease increases the potential for improving early diagnosis of demyelinating diseases of the MS spectrum in children.

2. The results contribute to reducing diagnostic errors, earlier identification of at-risk patients, and timely initiation of pathogenetic therapy.

3. Systematization of data on the immunogenetic features of children with MS, based on analysis of the major histocompatibility complex DR genes and humoral immunity parameters, will allow more accurate approaches to predicting disease course to be developed.

4. Determination of the DRB1*15~DQA1*01:02~DQB1*06:02 haplotype will help neurologists diagnose the disease in a timely manner, prescribe targeted immunomodulatory therapy, and reduce the risk of early disability in children.

5. An implementation certificate was obtained confirming the introduction of the study results into clinical practice at the Aksai Clinic: the effectiveness of implementation is expressed in the early diagnosis of MS in children in the Kazakh population.

Personal Contribution of the Doctoral Candidate

All stages of the dissertation research, including the study design, data collection and processing, interpretation, formulation of the statements submitted for defense, conclusions and practical recommendations, were carried out independently by the author as part of the individual doctoral study plan.

Conclusions

1. A feature of MS in children is the development of monosymptomatic manifestations progressing to multifocal leukopathy, with characteristic MRI changes in the form of round hyperintense T2 lesions, predominantly periventricular in location. In leukoencephalitis, a reduction in brain volume was noted at later stages of the disease, while NMOSD was characterized by longitudinally extensive spinal cord demyelination and pronounced retinal changes (95%).

2. The presence of the DRB1*15 allele increases the risk of MS in children in the Kazakh population 7.7-fold (RR = 7.7) and in the Russian population 6.1-fold (RR = 6.1). The HLA-DR15 haplotype (DRB1*15~DQA1*01:02~DQB1*06:02) was found in linkage disequilibrium in 76.2% of children with MS.

3. MOG-IgG is a significant diagnostic and prognostic biomarker in children with juvenile MS (sensitivity 40.5%, specificity 65%), enabling its use in comprehensive diagnostics for timely initiation of targeted therapy.

4. Medical and social analysis revealed a critically low level of parental awareness of the initial manifestations of demyelinating processes, leading to delayed presentation and delayed initiation of therapy in 75% of cases. At onset, 80% of children with juvenile MS and 95% of patients with NMOSD present with pronounced visual impairment, often misinterpreted as an isolated ophthalmological condition.

5. The developed comprehensive diagnostic algorithm, incorporating history-taking together with clinical, neuroimaging, neuro-ophthalmological and genetic data as well as serological markers, enables early diagnosis of MS and timely therapy, preventing irreversible loss of brain volume and progression of disability on the EDSS scale.

Approbation of the Dissertation Results

The main statements of the dissertation were presented and discussed at:

- 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 10–12 October 2018, Berlin, Germany.
- International Scientific and Practical Conference “Young Researcher: Challenges and Prospects for the Development of Modern Pediatrics and Pediatric Surgery”, 1 March 2019, Almaty, Republic of Kazakhstan.
- International Scientific and Practical Conference “Integration of the Fundamental Sciences and Applied Sciences in the Paradigm of a Post-Industrial Society”, 24 April 2020, Barcelona, Spain.

Publications

A total of 8 papers have been published on the topic of the dissertation:

1 article in a journal indexed in the Scopus database (Q2, Medicine). At the time of publication in 2022, “The Open Neurology Journal” had a 2020 CiteScore of 1.4; percentile in Psychiatry and Mental Health – 36; percentile in Neurology (clinical) – 26:

- Galym A. et al. Clinical and Genetic Analysis in Pediatric Patients with Multiple Sclerosis and Related Conditions: Focus on DR Genes of the Major Histocompatibility Complex. The Open Neurology Journal, 2022, Vol. 16, e1874205X2207200. DOI: 10.2174/1874205X-v16-e2207200.

3 articles in journals recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan:

- Galym A.G., Idrissova Zh.R. Features of the development of demyelinating diseases of the multiple sclerosis spectrum in children // Vestnik KazNMU. 2019. No. 1;
- Galym A. et al. Optimizing diagnostic pathways for children with suspected demyelinating diseases. Cent Asian J Med Hypotheses Ethics. 2025;6(4):318–325. doi:10.47316/cajmhe.2025.6.4.08;
- Galym A. et al. Assessment of parental perception of the health of children with demyelinating diseases: results of a survey. J Health Dev. 2026, 61(1), jhd055. doi:10.32921/2663-1776-2026-61-1-jhd055.

4 papers in the proceedings of international conferences:

1. ECTRIMS, 10–12 October 2018.
2. “Young Researcher: Challenges and Prospects for the Development of Modern Pediatrics and Pediatric Surgery”, 1 March 2019.
3. Modern Science. Management and Standards of Scientific Research – “Multiple Sclerosis in Children in Kazakhstan”, 18–19 May 2020.
4. “Integration of the Fundamental Sciences and Applied Sciences in the Paradigm of a Post-Industrial Society”, 24 April 2020, Barcelona, Spain.

Scope and Structure of the Dissertation

The dissertation consists of an introduction, four main sections, a conclusion, a list of findings and practical recommendations, and a list of references comprising 226 entries.

The dissertation is presented on 122 pages of typescript, illustrated with 22 tables and 6 figures, and includes 2 appendices.