ORIGINAL ARTICLE

Exploring the Role of MEFV Gene Mutations in Pediatric Drug-Resistant Epilepsy

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ABSTRACT

Objectives: Despite the advancements in antiepileptic drugs over the past decades, drug-resistant epilepsy (DRE) remains a significant challenge, particularly in children. Familial Mediterranean fever (FMF), attributed to mutations in the Mediterranean fever (MEFV) gene, has been linked to various neurological disorders, including seizures. This study investigates the potential association between MEFV gene mutations and DRE and evaluates their impact on the disease course.

Materials & Methods: A case-control study was conducted involving 22 children under 18 years of age with DRE, referred to the Pediatric Neurology Clinic of Children's Medical Center, Tehran, Iran, between March 2021 and March 2022. The control group comprised 30 healthy individuals randomly selected from the FMF database of Ardabil University, Iran. Relevant information, including age, demographics, disease characteristics, and treatment details, was collected using a structured form. Blood samples were analyzed for 12 common MEFV gene mutations.

Results: Out of 52 subjects, the case group consisted of 22 children diagnosed with DRE, compared to 30 patients without FMF in the control group. The mean age of the case group was 9.2 ± 4.5 years, with a mean age at seizure onset of 38.13 ± 32.21 months. MEFV mutations were identified in eight patients (15.4%), with seven in the control group and one (4.5%) in the case group. However, the difference in MEFV gene mutations between the case and control groups did not reach statistical significance (P=0.13).

Conclusion: The prevalence of MEFV gene mutations in children with DRE was 4.5%, suggesting that these mutations may not significantly influence the occurrence of DRE in this population.

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Introduction

Epilepsy is one of the most common neurological disorders worldwide, characterized by recurrent, uncontrolled seizures. These episodes can range from mild and infrequent to chronic, severely impacting one's quality of life. Despite advancements in modern antiepileptic drugs (AEDs), an estimated 20-30% of patients continue to experience drug-resistant epilepsy (DRE), remaining unresponsive to treatment (1). DRE is characterized by the inability to attain prolonged seizure freedom despite adequate trials of two well-tolerated and suitably selected antiseizure drugs (2). DRE cases are burdensome on the healthcare system because of the medical, psychological, and even financial costs they impose on patients (3, 4). One of the key aspects within this population that is of interest is the role that genetics plays in epilepsy, specifically DRE, where most treatment fails to work. The increased understanding over the last several years of the genetic aspects of specific epileptic syndromes

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poses both a challenge and an opportunity for devising treatment systems (5, 6).

Even though a significant amount of information is available concerning epilepsy, there remains an understanding gap in the genetics behind DRE, primarily the role of specific gene alterations (7, 8). The MEFV gene associated with familial Mediterranean fever (FMF), an auto-inflammatory condition, has become a potential contributor to shaping seizure disorders, particularly in children (9). Undoubtedly, some investigators propose that MEFV gene mutations may increase inflammation and seizure risk, but no mechanism is proposed. Because epilepsy has also been associated with several neurological manifestations and seizures in FMF, how the mutations in MEFV are involved in the drug resistance mechanism in epilepsy remains largely an unsolved question. Furthermore, this has not been studied extensively, even though MEFV mutations are described in some ethnic groups susceptible to FMF. Accordingly, this study seeks to fill this gap by examining the mutation of the MEFV gene in children with DRE and providing additional knowledge on this complex relationship (10, 11).

This study offers a fresh perspective on the link between genetic mutations and epilepsy, focusing specifically on the MEFV mutation in children with DRE. For the most part, other studies focused on the FMF inflammatory processes and further genetic associations with seizure (12). By concentrating on a particular gene mutation and its role in drug resistance, this study aims to improve individual treatment for epilepsy. Comprehending the genetic basis of drug resistance may enable more focused therapeutic interventions, potentially avoiding the empirical trial-and-error approach to defining epilepsy treatment. Furthermore, the results of this study can help at-risk youngsters receive more sensitive diagnostic testing, improving their prognosis.

Materials & Methods

A case-control study approach was used to assess the occurrence of the MEFV gene mutation among children with DRE compared to those in a control group. The case group comprised children diagnosed with DRE referred to the Pediatric Neurology Clinic at the Children's Medical Center, Tehran, between 2021 and 2022. DRE was described as the state in which sustained seizure-free status was not achieved after two or more AEDs were used. Patients with metabolic diseases, structural brain damage, intellectual disability, or developmental delay from a prenatal or perinatal cause were excluded from the study to select only primary cases of DRE. Based on the findings of the study by Salehzadeh et al., considering a prevalence of 2.7% and 1.6% of seizures in MEFV + and MEFV- patients, respectively, and taking α at 0.05 and power at 0.8, the minimum required sample size of this group was calculated to be 21 cases. For the control group, 30 individuals from the FMF registry data at Ardabil University who had no personal history of FMF or epilepsy and had no first-degree relatives having these conditions were selected. Since genetic testing for the MEFV gene is not sensitive to age variables, age compatibility between the case and control groups was excluded.

An average of 8 mL of blood was collected from each participant using EDTA tubes. The whole blood samples were collected under standard conditions and immediately transported to a reference laboratory specializing in genetic analyses, particularly MEFV mutation testing. The blood samples were cooled during the transportation phase. They were screened for the 12 known FMF mutations using a reverse hybridization technique, manufacturer's instructions (FMF StripAssay, Viennalab, Vienna, Austria) (13). These 12 genes were selected based on the 2012 consensus for appropriate genetic testing to investigate MEFV mutations, and were further supported by the frequency of mutations identified in subsequent studies (14).

Exons 2, 3, 5, and 10 were first amplified for each patient in a single and multiplex PCR using the primers that came with the RDB kit. The amplification program consisted of 35 thermocycling cycles (94°C for 15 seconds, 58°C for 45 seconds, and 72°C for 45 seconds) and a final extension at 72°C for 7 minutes. Four amplified DNA fragments, including 206, 236, 295, and 318 bp, were found by agarose electrophoresis, indicating the accuracy of the amplification. A test strip containing a parallel array of allele-specific oligonucleotide probes was used to selectively hybridize biotinylated PCR products. Twelve common mutations were identified as a result: M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H in exon 10, E148Q in exon 2, P369S in exon 3, and F479L in exon 5. These specific mutations were selected due to their known association with FMF and frequency in Mediterranean populations (13, 15).

Statistical Analysis

Descriptive statistics were employed to analyze demographic, clinical, and genetic information. For continuous data like age and duration of illness, means and standard deviations were utilized for description, whereas categorical variables were described using frequencies and percentages. A case-control comparison of MEFV mutation presence was carried

out through chi-square tests. Fisher's exact test was utilized to analyze the relationship between the status of mutation and seizure control because the sample size was small. Non-parametric variables were determined through the Mann-Whitney U test. Statistical analysis was performed on SPSS version 22 with the significance level at p-value < 0.05.

Ethical Considerations

The study strictly adhered to the guidelines outlined in the Helsinki Declaration. No intervention was performed besides routine care; all information was kept confidential. Informed consent was received from all participants or their authorized representatives before participation, with the right to withdraw from the study at any time without penalty. This study was approved by the Tehran University of Medical Sciences Ethics Committee, reference number IR.TUMS.CHMC.REC.1400.087.

Limitations

Several challenges were encountered during the study. First, due to ethical constraints, collecting blood samples from healthy children for the control group was impossible. Consequently, the control group was derived from an FMF registry, which, although comprehensive, was limited to individuals from a specific ethnic group. This limitation could potentially introduce bias into the genetic comparisons between the groups. To mitigate this, a random selection of controls was employed to enhance the sample's representativeness. Secondly, because of constrained financial resources, this study could not conduct whole genome sequencing for all patients; consequently, the researchers opted to conduct genetic analysis on the twelve most frequently reported mutations in the literature.

Results

The sample included 52 patients divided into two groups of 22 DRE patients (42.3%) and a control group of 30 patients (57.7%). The average age of the patient group was 9.2 years (SD = 4.5), ranging from 2.5 to 18 years. Thirty-two participants were male (61.5%), and 20 were female (38.5%). No difference was observed between the two genders in their distribution in the case and control groups. The average age of DRE onset in the patient group was approximately 38.1 months (SD = 32.2), spanning from 2 to 108 months. As for treatment, patients were on different antiepileptic drug (AED) treatment combinations: 13.6% were on two-drug therapy, 36.4% three-drug therapy, 31.8% four-drug therapy, and 18.2% five-drug therapy. In the DRE subgroup, 45.5% of patients had consanguineous parents, and 59.1% had a family history of epilepsy. The other symptoms included headaches (13.6%), paresthesia (9.1%), ataxia (4.5%), and fever (13.6%). The electroencephalogram (EEG) recording showed epileptic activity in 81.8% of the case group, while MRI scans were normal. Only 23.3% of the patients in the control group had mutations in some MEFV variants compared to the A744S variant mutation found in one patient (4.5%) of the drug-resistant epilepsy group, as illustrated in Figure 1.

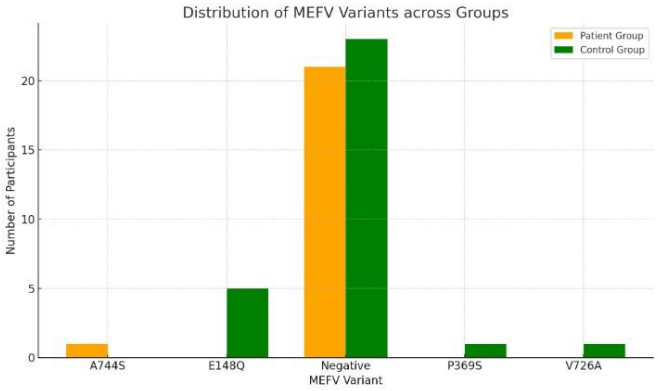

Figure 1. Comparison of the distributions of the MEFV genes found in the Case (orange) and Control (green) groups (Numbers in each group were described in the main text as shown in the figure).

Chi-square analysis was carried out to compare the MEFV mutation frequency between the control group and the DRE. Although the mutation rate in the control group was higher (23.3%) compared to the patient group (4.5%), this difference did not reach statistical significance (p = 0.11).

Discussion

The current study aimed to investigate the possible association between the MEFV gene and DRE in patients who were visited in a pediatric neurology clinic. Seizures could be one of the manifestations of FMF, although the prevalence is not as common as typical manifestations (16).

The MEFV gene on chromosome 16p13.3 consists of ten exons and encodes the pyrin protein. Pyrin, a 781-amino-acid protein, is a key regulator of the innate immune response and serves two primary functions: Modulating caspase-1 and IL-1β activation through its N-terminal PYD domain, exerting either pro-inflammatory or anti-inflammatory effects depending on the cellular context (17). Mutations in various exonic regions of the MEFV gene result in changes to the amino acid sequence of pyrin. These structural alterations are considered gain-of-function mutations, leading to enhanced pro-inflammatory activity of pyrin within the cell (18). Such dysregulation of pyrin's

inflammatory function ultimately manifests in autoinflammatory diseases such as FMF and Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND). Moreover, MEFV mutations have also been associated with other inflammatory conditions, including Behçet's disease, inflammatory bowel disease, and systemic juvenile idiopathic arthritis (sJIA) (18).

This study's first hypothesis was based on the shared inflammatory pathways, including the inflammasome, between FMF and DRE. FMF is a genetic autoinflammatory disease associated with mutations in the MEFV gene that encodes the pyrin protein, leading to increased IL-1β production (19). Although inflammation and febrile seizures have occurred in some IL-1β mutations with hippocampal sclerosis (20), in the present study, no favorable correlation was found between particular types of the MEFV gene (P369S, E148Q, V726A, A744S) and DRE.

Çomak et al. investigated the association between seizure and FMF disorder (21). The final results depicted a higher prevalence of febrile seizures in FMF patients. However, the final result could not determine whether this higher prevalence comes from febrile attacks or the patient's susceptibility. This study aimed to fill this gap, and it depicted that primary seizure disorder could not be attributed to FMF disorder.

Feld et al. investigated the neurological manifestations that could be directly related to FMF, associated diseases, and adverse effects of treatment (9). They mentioned several reports of EEG abnormalities in FMF patients, but no established relationship was observed between seizures and FMF. The research agenda in this study proposed further investigation, but this study's results revealed that even a genetic study could not prove this association.

Canpolat et al. reported a higher prevalence of seizure disorders in FMF patients (27.3%). EEG abnormalities were observed in all these patients (10). Notably, the study reported that two patients were diagnosed with FMF while under follow-up for epilepsy. The most common mutation among epileptic patients in this study was M694V, which was not found in the present study.

Biro et al.'s study concluded that febrile seizures are significantly higher in FMF patients in comparison with their healthy siblings (22). Two potential explanations exist for this finding. First, children with FMF experience frequent fever episodes and may have a higher susceptibility to febrile seizures during FMF attacks. Second, shared molecular mechanisms might account for the co-occurrence of FMF and febrile seizures. Mutations in the MEFV gene, resulting in a defective pyrin protein, lead to the activation of the pyrin inflammasome and elevated production of IL-1β. IL-1β is a well-established pyrogen implicated in developing simple febrile seizures. Notably, even asymptomatic carriers of MEFV mutations have been reported to exhibit an increased susceptibility to febrile seizures. (12, 19, 23). Following the primary goal of this study, the obtained findings did not support a significant association between DRE and FMF.

The current findings revealed a higher prevalence of epilepsy in children with consanguineous family histories, suggesting some genetic predisposition. Earlier reports by Asadi Pouya in Iranian children had revealed a higher parental consanguinity in epileptic cases compared to the population at large and had indicated familial risks (24). The obtained findings contradict those of Khan, who found no difference between parental consanguinity and epilepsy (25). These differences can be attributed to environmental, regional, and genetic factors, highlighting the need for more extensive studies to investigate these correlations adequately.

In Conclusion

The present research concludes that no correlation was observed between MEFV gene mutations and drug-resistant childhood epilepsy. As few as 4.5% of the affected group had MEFV mutations, and no statistical variation was found in the mutation frequency between patients and controls. Given the low prevalence and lack of statistical association, future research is suggested that targets other genetic factors and clinical features. Larger, ethnically mixed populations must replicate and expand these findings more broadly.

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Authors' Contribution

Vahid Ziaee conceptualized the study. Atefeh Habibi collected data, analyzed, and interpreted the results. Fatemeh Hadipour and Zahra Hadipour performed the genetic analyses. Reza Shervin Badv provided the study cases. Farhad Salehzadeh provided the control cases. Seyyed Reza Raeeskarami supervised the study. Payman Sadeghi prepared the

draft manuscript and revised it. All authors approved the final version of the article.

Conflicts of Interest

The authors reported no financial or non-financial conflict of interest.

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