



The impact of omega-3 on recurrent seizures in epileptic patients: A case study with evidence-based approaches

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Abstract

Background: Epileptogenesis is also associated with increased production of excessive pro-inflammatory cytokines which shows connection between pro-inflammatory cytokines as triggering factor with omega-3 which has anti-inflammatory effect. Omega-3, known for its neuroprotective and anticonvulsant properties, exhibits promising effects on epileptic seizure attacks.

Objective: This study aimed to evaluate the effect of omega-3 supplementation on the incidence of seizures in epilepsy patients.

Methods: This study used a literature search using advanced queries in the databases PubMed, Scopus, ProQuest, and Cochrane Library, and combined MeSH terms with Title/Abstract. The collected literature is discarded if there are duplicates, then literature is filtered that meets the eligibility criteria. We used the Oxford Center for Evidence-Based Medicine as a means of critical appraisal and determining the level of evidence of the selected literature.

Results: Four chosen literatures were critically assessed. Two articles indicating no significant difference between omega-3 and placebo and two articles showed had a significantly higher number of seizure-free days than placebo. The first article, involving 78 adults, reported a 50% reduction in seizure risk with a frequency RR of 0.57, 95% CI 0.19 to 1.75 (IS = 0%) indicating no significant difference between omega-3 and placebo groups after 12 weeks of treatment. The second study, comprising mostly non-significant findings, demonstrated no significant correlation between omega-3 and epilepsy attacks in epilepsy patients. The third literature revealed seizure occurrences per month in the EPA group (9.7±1.2), DHA group (11.7±1.5), and placebo group (16.6±1.5). Incidence rate ratio (IRR) adjusted for seizure type in EPA and DHA groups compared to the placebo group were 0.61 (CI = 0.42–0.88, p = 0.008, a 42% reduction) and 0.67 (CI = 0.46–1.0, p = 0.04, a 39% reduction), respectively. Both treatment groups had a significantly higher number of seizure-free days compared to the placebo group (p < 0.05). The fourth study reported intervention group frequency (4.72 ± 1.6, p= 0.014) and placebo frequency (11.64 ± 1.63, p=0.014) with intervention group seizure duration (6.64 ± 1.39, p=0.009) compared to placebo group (14.36 ± 2.18, p=0.009).

Conclusion: Omega-3 supplementation may be considered for management in patients with recurrent epileptic seizures, although its effect on reducing seizure frequency remains inconsistent.

Keywords: epilepsy, recurrent epilepsy, case study, omega-3 fatty acid

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Case report

A 20-year-old male, referred by a neurologist to a clinical nutrition specialist, has been diagnosed with symptomatic generalized tonic-clonic epilepsy. He has been struggling with recurrent seizures due to epilepsy since childhood. Vital signs and overall examinations are within normal limits. His present body mass index is 20.2 kg/m². Laboratory tests are within normal limits, and an EEG examination reveals abnormal epileptiform activity in the left temporal region, accompanied by a focal slowing in both temporal lobes, predominantly on the left. The patient is regularly taking antiepileptic medication, Levetiracetam 2x500 mg, and Paracetamol 1000 mg for headache pain as prescribed by his neurologist. Subsequently, after reading online about the potential benefits of omega-3 in reducing recurrent seizures in epilepsy patients, he inquired about the advantages of omega-3 for patients with epilepsy, such as himself.

Introduction

Epilepsy is a disorder caused by chronic brain abnormalities characterized by recurrent seizures due to paroxysmal changes in neurological function caused by excessive neuron discharge and hyper synchronization in the brain without identifiable precipitating factors.^{1,2} According to the World Health Organization (WHO), the global prevalence of epilepsy is approximately 50 million people. In affluent countries, a reckoned 49 per 100,000 individuals are diagnosed with epilepsy per year, at the same time in low- and middle-income countries, it reaches 139 per 100,000 population.³ In Indonesia, the prevalence of epilepsy is around 8.2 per 1,000 population, with around 50 new cases per 100,000 population yearly.⁴ Patients with recurrent epileptic seizures may experience disruptions in daily activities, impacting the overall quality of life for individuals with epilepsy.^{5,6}

Epilepsy occurs when neurons in the epileptogenic focus have a lessened stimulus threshold, making the irritated neurons easily triggered by physiological changes that as fatigue,

lack of sleep, stress, fever, constipation, structural disorders, infections, or metabolic disturbances. In adults without a genetic predisposition to epilepsy, usual etiologies for seizures include encephalitis/meningitis, traumatic brain injury, and brain tumors.⁷ The pathophysiology of epilepsy arises from an imbalance between excitatory and inhibitory stimuli in the epileptic focus. When excitatory stimuli exceed inhibitory stimuli, abnormal high depolarization occurs, causing a series of action potentials. Known processes contributing to neuronal depolarization include calcium and sodium influx, potassium efflux, excitation through amino acids (such as glutamate), and inhibition through neurotransmitters (GABA). Epileptogenesis is also associated with increased production of excessive pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin-6 (IL-6).^{8,9} Epilepsy treatments, including phenytoin, carbamazepine, and valproic acid, along with non-pharmacological interventions such as lifestyle modifications, and an area still under investigation is the administration of anti-inflammatory supplements like omega-3 to control seizures.¹⁰

Omega-3 fatty acids are polyunsaturated fatty acids with multiple double bonds. The three most crucial omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which cannot be endogenously synthesized and must be obtained from dietary sources. Omega-3 fatty acids play a functional role in physiological processes within the brain.¹¹ In epilepsy, omega-3 can reduce inflammation by inhibiting the formation of pro-inflammatory eicosanoids (EPA), suppressing NF- κ B, and decreasing the release of pro-inflammatory cytokines such as TNF- α . EPA can reduce the expression of TNF- α , IL-6, and prostaglandin E, and suppress TNF- α and IL-6 in hepatocytes.¹²

Research demonstrating the effects of omega-3 supplementation in reducing the frequency and duration of seizures in patients with refractory epilepsy includes a study by Omrani et al.¹³ In this study, 50 patients with refractory epilepsy were divided into two groups,

placebo, and control, with the control group receiving omega-3 fatty acid capsules containing 120 mg DHA and 180 mg EPA twice daily. Patients receiving omega-3 did not experience seizures significantly during the study period, and the levels of TNF- α and IL-6 decreased by 38% and 41%, respectively. This contrasts with a systematic review study by Pourmasoumi et al.,¹⁴ which involved several studies that did not show a notable relationship between omega-3 and epilepsy attacks in epilepsy patients.

Based on previous research, it is not yet conclusive whether omega-3 can reduce seizure frequency in epilepsy patients. This evidence-based case report seeks to assess the impact of omega-3 supplementation on seizure attacks in epilepsy patients.

Clinical questions

"Can omega-3 reduce seizure episodes in adult and children patient with epilepsy?"

Participants (P): adult and children patient diagnosed with epilepsy

Intervention (I): omega 3 supplementation

Control (C): placebo

Outcome (O): seizure episodes

Methods

Searching strategy

A literature search was managed using an advanced search with a combination of MeSH Terms and Titles/Abstracts in four databases: PubMed, Cochrane Library, Scopus, and Proquest. Keywords included "epilepsy," "epilepsy syndrome," "omega-3," "omega-3 eicosapentaenoic," "omega-3 fatty acid," "n-3 unsaturated fatty acid," "placebo," and "epileptic seizure." The Oxford Centre for Evidence-Based Medicine guidelines were utilized for critical literature assessment and determining the level of evidence.

Eligibility criteria

Inclusion criteria: 1) adult and children diagnosed with epilepsy; 2) patients receiving omega-3 supplementation; 3) research outcome focusing on seizure episodes; 4) study design being a controlled clinical trial or a systematic review/meta-analysis of randomized controlled trials; 5) articles published in English.

Exclusion criteria: 1) studies not conducted on humans; 2) articles not available in full text.

Results

The selected articles met eligibility criteria through systematic reviews, meta-analyses, and controlled clinical trials. Inclusion criteria were as follows: 1) epilepsy patients, 2) utilization of omega-3 supplementation, 3) research outcomes indicating a reduction in seizure frequency, 4) articles adopting systematic review-meta-analysis or randomized controlled trials (RCT) study designs, 5) articles written in English, and 6) research involving human subjects. Exclusion criteria included articles lacking full text. The literature search was independently conducted across four databases: PubMed, Cochrane Library, Embase, and ProQuest. The literature search process is depicted in Figure 1. Keywords employed were "epilepsy," "epilepsy syndrome," "omega-3," "omega-3 eicosapentaenoic," "placebo," and "epileptic seizure." Additionally, a review using Mendeley was performed subsequently to exclude duplicate articles. The research will be critically assessed using the Oxford Centre of Evidence-based Medicine (CEBM) critical appraisal tool for systematic reviews and meta-analyses by two authors. This assessment evaluates the aspects of study validity, significance, and applicability. This study obtained literature from PubMed (3 articles), Cochrane Library (2 articles), ProQuest (1 article), and Scopus (8 articles) as shown in **Table 1**. Duplicate screening was conducted using Mendeley. Subsequent screening was based on methods, title-abstract, PICO criteria, and full-text availability. The screening results are illustrated in **Figure 1**.

Table 1. Literature searching strategy

Database	Search Strategy	Hits
Pubmed	(((((epilepsy[Title/Abstract]) OR (epilepsy[MeSH Terms])) OR (epilepsy syndrome[Title/Abstract])) OR (epilepsy syndrome[MeSH Terms])) AND (((omega 3[Title/Abstract]) OR (omega 3[MeSH Terms])) OR (omega 3 eicosapentaenoic acid[Title/Abstract])) OR (omega 3 eicosapentaenoic acid[Title/Abstract]))	3
Cochrane	ID Search Hits #1 (epilepsy):ti,ab,kw (Word variations have been searched) #2 (epilepsy syndrome):ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Epilepsy] explode all trees #4 #1 OR #2 OR #3 #5 ("omega 3 fatty acids"):ti,ab,kw (Word variations have been searched) #6 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees #7 #5 OR #6 #8 ("placebo"):ti,ab,kw (Word variations have been searched) #9 MeSH descriptor: [Placebos] explode all trees #10 #8 OR #9 #11 (epileptic seizure):ti,ab,kw (Word variations have been searched) #12 MeSH descriptor: [Seizures] explode all trees #13 #11 OR #12 #14 #4 AND #7 AND #10 AND #13	2
Scopus	TITLE-ABS-KEY (epilepsy) OR TITLE-ABS-KEY (epilepsy AND syndrome) AND TITLE-ABS-KEY (omega 3) AND TITLE-ABS-KEY (placebo) AND TITLE-ABS-KEY (epileptic AND seizure)	8
ProQuest	title(epileptic seizure) AND title(omega 3)	1

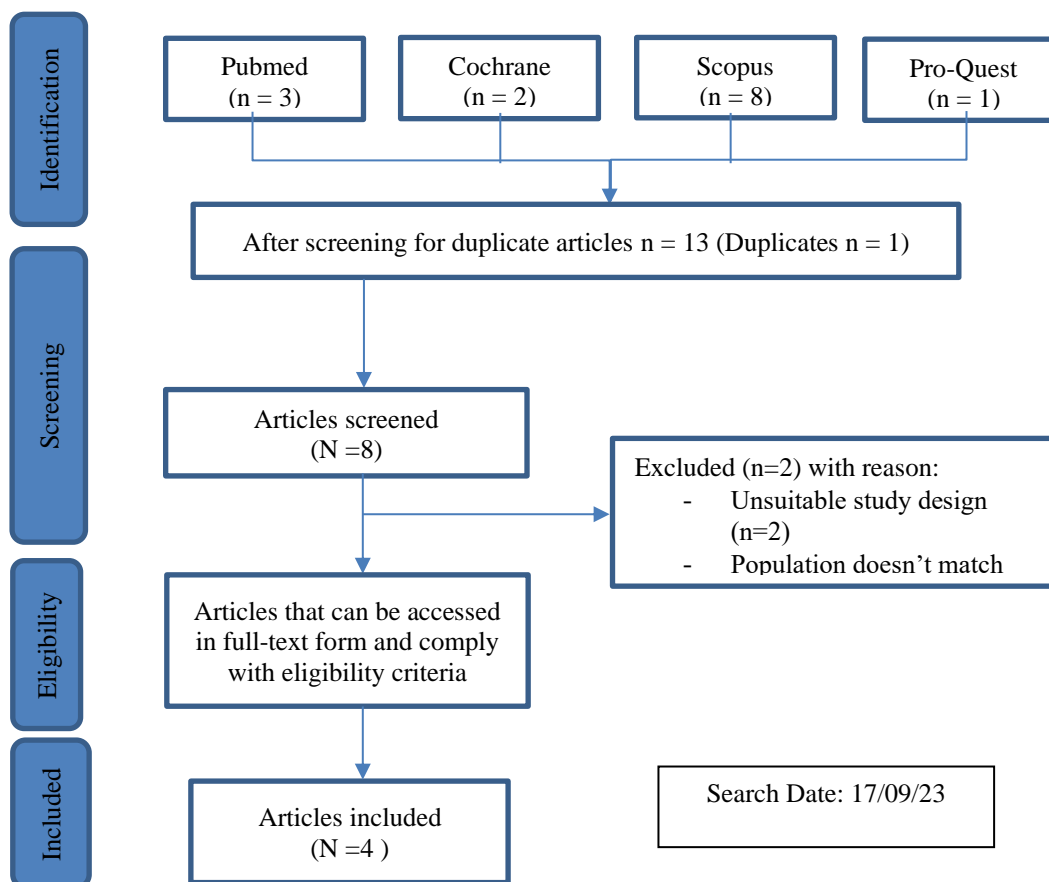


Figure 1. Prisma's flow chart

Table 2. Characteristics of the study

Researcher	Design	Population/Intervention	Research result
Vancelos, et al., (2016) ¹⁵	Systematic review/Meta-Analysis of Randomized Controlled Trials consisting of 3 RCT. ¹⁵	RCT: Adult and pediatric epilepsy patients taking Omega-3 supplementation.	The average frequency of seizures, other side effects, and secondary effects, namely Quality of Life in Epilepsy (QOLIE-31).
Pourmasoumi, et al., (2018) ¹⁴	Systematic review/Meta-Analysis of Randomized Controlled Trials consisting of 9 RCTs.	RCT: Nine articles with 230 patients. The intervention group received Omega-3 fatty acid supplements (1100 mg/day) with doses of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and alpha-linolenic acid (5 g/day). And in other studies, it contains 565 mg EPA/day. The average duration of the study was 22 ± 15.27 weeks.	Epileptic attacks.
Ibrahim, et al., (2018) ¹⁶	Randomized Double-Blinded Controlled Trial	Ninety-nine (n = 99) subjects with drug-resistant epilepsy (DRE), aged 5–16 years (n = 85) and 17–45 years (n = 14). After randomization, subjects were given two, four, or six DHA capsules per day (417.8 mg DHA and 50.8 mg EPA/capsule, n = 33), EPA (385.6 mg EPA and 81.2 mg DHA/capsule, n = 33), or placebo (high oleic acid sunflower oil, n = 33) for one year.	Seizure incidence, seizure incidence rate ratio (IRR) adjusted for seizure type, difference in IRR between EPA and DHA groups, and number of seizure-free days.
Omrani, et al., (2019) ¹³	Randomized Triple-Blinded Controlled Trial	50 patients with recurrent epileptic seizures. The intervention group received omega-3 FA supplementation, 180 mg eicosapentaenoic acid (EPA), and 120 mg docosahexaenoic acid (DHA), and the control group received placebo capsules given twice a day to each group for 16 weeks.	Frequency and duration of seizures in the intervention group compared to the placebo group.

Table 3. Validity criteria for the studies by Vancelos et al. and Pourmasoumi et al.

	Study Design	Question	Find	Appraise	Inclusion	Total Up	Heterogeneity	Result	Applicability	Level of evidence
Vasconcelos, et al., (2016) ¹⁵	Systematic Review / Meta-Analysis of Randomized Controlled Trials	+	+	+	+	+	+	A	-	Level 1A
Pourmasoumi, et al., (2018) ¹⁴	Systematic Review / Meta-Analysis of Randomized Controlled Trials	+	+	+	+	+	+	B	-	Level 1A

A = In a study involving 78 adults, the risk of seizures was reduced by 50%. frequency was RR 0.57, 95% CI 0.19 to 1.75 (IS = 0%) indicating no significant difference between omega-3 and placebo groups, after 12 weeks of treatment. The estimated 50% reduction in seizure frequency after 12 weeks in a study involving single children was RR 33.00 (95% CI 4.77 to 228.15) indicating a significant difference favoring the PUFA group. B= The majority of included studies did not show a significant association between omega-3 and epileptic seizures in epilepsy patients.

Table 4. Validity criteria for the studies by Ibrahim et al. and Omrani et al.

Article	Study Design	Randomization	Similarity	Equally treated	Intention to treat analysis	Blinding	Result	Applicability	Level of evidence
Ibrahim, dkk., (2018) ¹⁶	Randomized Controlled Trials	+	+	+	+	Double-blind	C	+	Level 1B
Omrani, dkk., (2019) ¹³	Randomized Controlled Trials	+	+	+	+	Triple-blind	D	+	Level 1B

C = Seizures occurred in 59 subjects (n = 59) (59.6%). The mean number of seizures per month was 9.7 ± 1.2 in the EPA group, 11.7 ± 1.5 in the DHA group, and 16.6 ± 1.5 in the placebo group. The seizure incidence rate ratio (IRR) adjusted for seizure type in the EPA and DHA groups compared with the placebo group was 0.61 (CI = 0.42–0.88, p = 0.008, there was a 42% reduction) and 0.67 (CI = 0.46–1.0, p = 0.04, 39% reduction). There was no difference in IRR between the EPA and DHA groups (p=0.56). Both treatment groups had a significantly higher number of seizure-free days compared to the placebo group (p < 0.05). D= Frequency of the intervention group (4.72 ± 1.6 , p= 0.014) and placebo with frequency (11.64 ± 1.63 , p=0.014) and duration of seizures in the intervention group (6.64 ± 1.39 , p=0.009) compared to the placebo group (14.36 ± 2.18 , p=0.009).

Discussion

The literature search yielded four studies that met the criteria. Vasconcelos et al. directed a systematic review and meta-analysis, including three selected studies: Research by Bromfield's¹⁵ in 2008 research on 27 American adults divided into intervention (2.2 g/day omega-3, EPA: DHA

ratio 3:2) and placebo groups, research by Yuen's¹⁵ in 2005 study on 58 individuals in the UK divided into intervention (1.7 g/day omega-3, 1g EPA and 0.7g DHA) and placebo groups, and Reda's (2015) research on 70 Egyptian children divided into intervention (3 ml/day fish oil 1200 mg, 0.24 g DHA and 0.36 g EPA) and placebo groups. All participants received interventions for

12 weeks. The study aimed to assess the benefits of Omega-3 supplementation in controlling seizures and improving the quality of life. Exclusion criteria included non-RCT studies, studies reporting only biochemical results without clinical outcomes, and incomplete data. Bias risk was assessed based on the Cochrane Handbook for Systematic Reviews of Interventions by Higgins¹⁵ in 2011 for RCT studies.

Three RCTs investigating the effects of Omega-3 supplementation on epilepsy included a total of 155 subjects (85 adults and 70 children); 78 (43 adults and 35 children) were randomized to receive omega-3, and 77 (42 adults and 35 children) to receive placebo. Only one study, consisting solely of children, reported seizure freedom with omega-3 supplementation. The estimated risk for this outcome was noteworthy higher for children receiving omega-3 contrasted to the control group (risk ratio (RR) 20.00, 95% confidence interval (CI) 2.84 to 140.99, 1 study, 70 children). Likely, omega-3 supplementation was linked with a significant difference in the proportion of children with at least a 50% reduction in seizure frequency (RR 33.00, 95% CI 4.77 to 228.15, 1 study with high risk of bias, 70 children). However, this effect was not examined when data from two studies, including adult participants, were combined (RR 0.57, 95% CI 0.19 to 1.75, I² 0%, 2 studies, 78 participants, low-quality evidence). No significant differences were found between omega-3 and the control group regarding gastrointestinal effects (RR 0.78, 95% CI 0.32 to 1.89, 2 studies, 85 participants, low-quality evidence). Omega-3 supplementation did not result in considerable differences in average seizure frequency, quality of life, or side effects. This suggests that omega-3 may significantly reduce seizure freedom in children with epilepsy. However, there is insufficient evidence to support the use of omega-3 supplementation in adults with refractory epilepsy. This study need further trials with larger sample sizes to judge the benefits of omega-3 supplementation in the treatment of epilepsy with drug-resistant.¹⁵

Pourmasoumi et al.¹⁴ conducted a systematic review and meta-analysis, identifying nine

clinical trial articles published between 2002 and 2015, involving 205 epilepsy patients. DeGiorgio¹⁴ in 2015 used low-dose fish oil (1080 mg/day) and high-dose fish oil (2160 mg/day) in epilepsy patients with an average age of 33 ± 10.33 years over 42 weeks. About 25% of participants in the low-dose fish oil group showed a 50% reduction in frequency of seizure, while 15% of high-dose fish oil participants exhibited a similar reduction compared to the placebo. About 10% of participants became seizure-free with low-dose fish oil during the intervention. No association between fish oil and seizure severity scores was found. Schlanger¹⁴ in 2002 administered omega-3 supplemented bread (5 g) containing 46% DHA, 18% EPA, and 1% ALA, plus Vitamin E (100 IU) to alleviate seizures in epilepsy patients with an average age of 19 years over 24 weeks. Nonetheless, this study estimated only five patients without a control group and had a Jadad score of 0, precluding conclusions about the positive effects of omega-3.¹⁴

From the results of Yuen's¹⁴ in 2005 research, it is known that patients who consumed capsules containing 1000 mg of fish oil (171 mg EPA, 112 mg DHA, <100 IU Vitamin A, and <40 IU Vitamin D) for 12 weeks experienced fewer seizures in the first 6 weeks, although this decrease was not consistent in the second 6 weeks. Research by Bromfield¹⁴ in 2008 studied epilepsy patients with an average age of 36 years in the omega-3 group and 38 years in the placebo group for 4 weeks. The study revealed that patients in the intervention group (omega-3 supplement: EPA plus DHA, 2.2 mg/day with a ratio of 3:2) did not experience a reduction in seizures. The mean frequency of seizure increased to 6% in the omega-3 group and decreased to 12% in the placebo group ($P = 0.21$). In a 30-week crossover study, research by DiGiorgio¹⁴ in 2008 administered eight capsules containing 1200 mg of fish oil per day (216 mg EPA and 144 mg DHA) to patients (mean age 41.5 years). This study demonstrated an increase in seizure frequency of 11% in the intervention group and 14% in the placebo group ($P = 0.051$), without a significant decrease in the frequency of seizures. The severity of Seizure, calculated using the

National Hospital Seizure Severity Scale, showed a non-significant decrease in mean scores from 8.55 to 7.55 in the fish oil group and from 8 to 7.57 in the placebo group.¹⁴

Research by Yuen¹⁴ in 2012 evaluated the effects of 1000 mg EPA and 20 mg mixed tocopherols over 12 weeks in epilepsy patients with an average age of 49 years. The median seizure frequency reduced from 15 to 11, but it was not statistically remarkable ($P = 0.26$). The study concluded that there was no significant association between EPA supplement consumption and seizure frequency. In Puri's¹⁴ research in 2007, patients got three capsules containing 1000 mg fish oil (171 mg EPA, 112 mg DHA, <100 IU Vitamin A, and <40 IU Vitamin D) twice daily for 12 weeks. The average age of patients in the intervention and placebo groups was 50.7 ± 13.6 years and 40.5 ± 12.0 years, respectively. The results indicated that omega-3 supplementation led to biochemical changes, likely a less in phosphodiester percentage (average 3.75 ± 2.81), an expansion in gamma-nucleotide triphosphate percentage (average 1.73 ± 2.41), and an improvement in broadband components (BBC) (average 13.56 ± 7.74) to evaluate brain biochemical changes potentially related to epilepsy. The study concluded that there was no connection between biochemical changes on epileptic seizures.¹⁴

Research conducted by Dahlin¹⁴ in 2007 was conducted on 25 children with an average age of 6.3 ± 4.2 for 12 months. 1-2 g of liquid fish oil is given and given 4 times a day. The results of the study showed that 16 children (after 3 months), 15 children (after 6 months), and 12 children (after 12 months) experienced a reduction in seizures of >50%. In serum, an increase in EPA and linoleic acid levels, a decrease in arachidonic acid (AA), and a slight increase in DHA were found. However, no association was found between changes in serum fatty acids and seizure response.¹⁷

Research conducted by Reda¹⁴ et al. in 2015 in participants, the age of the intervention group was 6.9 ± 2.5 years and the age of 6.6 ± 2.4 years in the control group. This study used a daily dose of 3 mL containing 1200 mg of fish oil, providing

240 mg DHA and 360 mg EPA, plus Vitamin E for the intervention group, and 3 mL of corn oil daily for the control group in the study. After 12 weeks, the results showed that the frequency and severity of seizures decreased in the intervention group. Omega-3 is known to increase the seizure threshold in epilepsy patients, thereby effectively controlling the occurrence of seizures among the nine studies, research by Yuen¹⁴ in 2005, DeGiorgio¹⁴ in 2015, Schlanger¹⁴ in 2002, and Reda¹⁴ in 2015 indicated a remarkable positive correlation between omega-3 fatty acids and epileptic seizures. Despite that, the strength and quality of these studies remain low, preventing a conclusive determination of the positive outcome of omega-3 on seizure frequency. Studies by Dahlin¹⁴ in 2007, DeGiorgio¹⁴ in 2008, Puri¹⁴ in 2007, Bromfield¹⁴ in 2008, and Yuen¹⁴ in 2012 did not demonstrate significant effects. Therefore, this study need research with large sample size and a long follow-up period to clarify the impact and determine the underlying mechanisms with comprehensive data.¹⁴

According to previous research by Bazan et al.¹⁸, two distinct pathways explain the effects of omega-3 on epileptic seizures. The first mechanism involves DHA regulating glutamate transporters (GLT) such as GLT1. The dysregulation of these transporters reduces glutamate concentrations, thus preventing the onset of seizures. The second mechanism, through Neuroprotectin D1 (NPD1), a derivative of DHA, exerts protective effects on the central nervous system (CNS). NPD1 enhances anti-apoptotic proteins, reduces pro-apoptotic proteins, and mitigates the effects of astrocytes and pro-inflammatory cytokines, which may lead to seizures.¹⁸ According to Kavyani et al., omega-3 has an anti-inflammatory effect in reducing pro-inflammatory cytokines such as C-reactive protein, TNF- α , and IL-6.^{19,20}

From the RCT study by Ibrahim et al.¹⁶, it was found that compared to the control group, the administration of omega-3 supplementation (DHA and EPA) in patients with drug-resistant epilepsy resulted in a longer duration of seizure-free days than the placebo group ($p < 0.05$). This favorable effect of omega-3 on epilepsy is

associated with anti-excitatory and neuroprotective mechanisms. Omega-3 can reduce neuronal electrical activity, and inhibit repetitive stimulatory activities in cells, thus impeding the occurrence of epileptic crises. The anti-excitatory effect of omega-3 is related to the partial inhibition of ion channels on cell membranes, reducing the influx of sodium and calcium ions into cells.²¹ Omega-3 is a crucial structural component of nerve membranes and is involved in regulating nerve functions. It diminishes the production of reactive oxygen species, byproducts of energy metabolism that can cause oxidative damage to phospholipid membranes, contributing to inflammation and neurodegeneration, thereby preventing epileptic seizures.²² Additionally, omega-3 inhibits the synthesis of cyclooxygenase-2 (COX-2), an enzyme involved in pro-inflammatory production.¹⁷ Omrani et al.¹³'s study further proves that omega-3 supplementation has the effect of elevating the seizure threshold in the supplementation group compared to the placebo. Omega-3 reduces inflammation by inhibiting pro-inflammatory cytokines, namely IL-6 and TNF- α , in macrophages and hepatocytes. The expression of IL-6 and TNF- α cytokines in astrocytes may cause a decrease in seizure threshold and an increase in seizure frequency. TNF- α may induce hyperexcitability of neuronal through changes in ion channels and production of glutamate, resulting in membrane depolarization and recurrent seizures.¹³

The four studies conducted by Vasconcelos et al.¹⁵ in 2016, Pourmasoumi et al.¹⁴ in 2018, Ibrahim et al.¹⁶ in 2018, and Omrani et al.¹³ in 2019 exhibit strengths and limitations. In Vasconcelos et al.¹⁵'s study in 2016, limitations include the inclusion of only a few studies in the meta-analysis, small sample sizes, and insufficient evidence supporting the supplementation of omega-3 in individuals with refractory epilepsy. Further trials are necessary to assess the benefits of supplementation of omega-3 in the treatment of epilepsy with drug-resistant (referred to specific type of epilepsy). Research results of Pourmasoumi et al.¹⁴ in 2018 stated that most studies do not show a significant

relationship between omega-3 and epileptic seizures in epilepsy patients. So the benefits of omega-3 fatty acids that can have a positive effect on epilepsy patients are still controversial. Further research is needed to clarify the impact of omega-3 and determine the mechanism. future studies should use more comprehensive data, larger sample sizes, and long-term follow-up periods.

Ibrahim et al.¹⁶'s study in 2018 faces limitations such as heterogeneity in the study population concerning the frequency and types of seizures referred to specific type of epilepsy (drug-resistant epilepsy), dependence on patient-reported seizure frequency data to assess the impact of omega-3 supplementation, prolonged study duration leading to some patients discontinuing recommended antiepileptic medications, and a lack of examination of inflammatory markers due to limited research funds. This study was conducted on Sudanese patients with a traditional diet low in n-3 fatty acids. Omrani et al.¹³'s study in 2019 has limitations as it does not assess plasma levels of DHA and EPA in both placebo and supplemented patients before and after treatment. The small sample size is also a constraint in this research.

In the case presented, a 20-year-old male with epilepsy shares similarities in identity and diagnosis with the subjects discussed in the research. The patient can be given omega-3 supplementation to reduce seizure frequency. EPA and DHA are considered safe up to 5 g/day according to the European Food Safety Authority, and up to 3 g/day according to the US-American Food and Drug Administration. The FDA recommends that consumption of these supplements not exceed 3 grams of combined EPA and DHA per day because it has a prolonged bleeding effect as well increased risk of atrial fibrillation.^{23,24} It safe to advise EPA: DHA ratio 1.5:1.^{25,26} EPA:DHA ratios showed that a balanced 1:1 diet was the most effective combination to mitigate inflammation, oxidative stress and metabolic disorders.²⁷ It is advisable to recommend the consumption of omega-3-rich foods, including salmon, mackerel, tuna, herring, and sardines.²⁸

Conclusion

Omega-3 supplementation can serve as adjunctive therapy for patients experiencing recurrent epileptic seizures. Based on a critical review conducted in two meta-analyses and two randomized controlled trials (RCTs), omega-3 supplementation can provide benefits for neuroprotective and antiepileptic functions, as well as reduce inflammation that may lead to recurrent seizures in epilepsy patients. Omega-3 doses can be given in adults and children in low doses of around 1200 mg of fish oil per day (240 mg EPA and 360 mg DHA) to patients for a minimum of 12 weeks to reduce the frequency of seizures. Further research is different methodologies and designs to prove the benefits of the administration of omega-3 in patients with recurrent epileptic seizures.

Conflict of interest

The authors declare that they have no competing interests.

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