A Mini Review of Doose Syndrome: Clinical Manifestations, Diagnosis, and Treatment

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SUMMARY

Doose syndrome, or myoclonic-astatic epilepsy (MAE), is a rare and complex epileptic encephalopathy that affects young children. Characterized by myoclonic-atomic seizures, generalized tonic-clonic seizures, and atypical absense seizures, the etiology of Doose syndrome is heterogeneous and involves both genetic and environmental factors. While advancements in genetic research have contributed to a better understanding of the syndrome, no major genetic factor has been identified, highlighting the need for further investigation. Diagnosis relies on thorough clinical evaluation, electroencephalographic findings, and, in some cases, genetic testing. Early diagnosis is critical, as some antiepileptic drugs may exacerbate the condition, while others can provide better seizure control. Treatment options include medications such as valproate, levetiracetam, and lamotrigine, ketogenic and modified Atkins diets, corticosteroids, and, in refractory cases, corpus callosotomy. Recent studies have also shown promise in using highly purified cannabidiol for the treatment of refractory epilepsy in Doose syndrome. Future research should focus on elucidating the genetic and environmental factors involved in the development and progression of Doose syndrome and identifying novel therapeutic targets. Additionally, further investigation of existing treatment options, including dietary therapies and highly purified cannabidiol, is necessary to optimize patient care and improve long-term prognosis for individuals affected by this rare and challenging epilepsy syndrome.

Introduction

Doose syndrome, also known as myoclonic-astatic epilepsy (MAE), was first described by German pediatric neurologist Herman Doose in 1970. This rare and complex form of epilepsy typically affects children aged one to five years (Kelley and Kossoff, 2010). The primary characteristic of Doose syndrome is the presence of
myoclonic-atactic seizures, which involve abrupt muscle contractions followed by a sudden loss of muscle tone. These seizures often lead to falls, posing a significant risk of injury for affected children (Dubru et al., 2002).

In addition to myoclonic-atactic seizures, children with Doose syndrome may experience other types of seizures, such as generalized tonic-clonic seizures, absence seizures, and atypical absence seizures (Inoue et al., 2014). Generalized tonic-clonic seizures involve a combination of muscle stiffening and rhythmic jerking, while absence seizures are characterized by brief lapses in consciousness. Atypical absence seizures, on the other hand, are similar to absence seizures but may last longer and exhibit more pronounced physical symptoms (Inoue et al., 2014).

The etiology of Doose syndrome remains incompletely understood, but genetic factors are believed to play a significant role in its development (Tang and Pal, 2012). Recent advancements in genetic research have uncovered potential gene mutations and chromosomal abnormalities associated with the syndrome. However, the exact genetic mechanisms and inheritance patterns have not yet been established, and environmental factors may also contribute to the development of the disorder (Tang and Pal, 2012).

Due to the heterogeneous nature of Doose syndrome and the multiple seizure types associated with it, diagnosis can be challenging. A comprehensive clinical evaluation, including a detailed patient history, physical examination, and electroencephalographic (EEG) findings, is essential for accurate diagnosis. In some cases, genetic testing may also provide valuable information (Inoue et al., 2014).

Understanding the underlying causes and mechanisms of Doose syndrome is critical for developing targeted treatments and improving outcomes for affected children. Although advancements have been made in recent years, further research is needed to fully comprehend the etiology and pathophysiology of this rare and complex form of epilepsy.

**Clinical Manifestations**

Children with Doose syndrome generally exhibit a sudden onset of seizures, often following a period of normal development (Inoue et al., 2014). These seizures, called myoclonic-astatic seizures, are characterized by sudden jerking movements, followed by loss of muscle tone, which can cause the child to fall (Tang and Pal, 2012). In some cases, the seizures can be frequent, occurring multiple times per day, and may be triggered by fever, illness, or other factors such as stress or sleep deprivation (Kelley and Kossoff, 2010).

In the early stages of the syndrome, cognitive development usually appears normal. However, as the condition progresses, many children with Doose syndrome may experience cognitive decline, including difficulties with learning, memory, and attention (Nickels et al., 2021). This decline can vary significantly from child to child, with some experiencing mild impairments and others experiencing more severe deficits (Moeller et al., 2014).

In addition to cognitive challenges, children with Doose syndrome may exhibit behavioral disturbances. These can include hyperactivity, irritability, aggression, and difficulties with social interactions (You et al., 2008). Sleep disturbances, such as insomnia or frequent night-time awakenings, may also be present, which can further exacerbate cognitive and behavioral issues (Stenger et al., 2017).
It is important to note that the clinical manifestations of Doose syndrome can be highly variable, and each child may experience a unique combination of symptoms and challenges. Early diagnosis and intervention are crucial to improve outcomes and minimize the impact of the condition on the child's quality of life (Trivisano et al., 2015).

**Diagnosis**

The diagnosis of Doose syndrome is a complex process that requires a comprehensive evaluation of clinical, electroencephalographic (EEG), and genetic findings (Oguni, 2022).

Clinical presentation: The revised diagnostic criteria for Doose syndrome emphasize the presence of myoclonic-atonic seizures, which are the hallmark of the condition. The age of onset usually falls between 7 months and 6 years (Oguni, 2022). Patients may also have a history of other generalized seizure types, including absence, tonic, and tonic-clonic seizures, which further supports the diagnosis. A detailed medical history, thorough physical examination, and careful observation of seizure characteristics can help clinicians identify the specific features of Doose syndrome.

EEG findings: Electroencephalography (EEG) is an essential tool in diagnosing Doose syndrome. It is used to record the electrical activity of the brain and detect any abnormal patterns. EEG findings in Doose syndrome typically show generalized spike-wave and polyspike-wave discharges, often with a normal background activity (Moeller et al., 2014). These discharges can be regular or irregular, and their frequency may range from 2.5 to 4 Hz. It is important to note that the EEG findings may evolve over time, and multiple EEG recordings may be necessary to confirm the diagnosis.

Genetic testing: Advances in molecular genetics have significantly contributed to our understanding of Doose syndrome, revealing several genes associated with this disorder (Table 1). These include CHD2, SCN1A, STX1B, and others (Trivisano et al., 2015; Vlaskamp et al., 2016). Genetic testing, employing techniques such as next-generation sequencing (NGS), whole-exome sequencing (WES), and targeted gene panels, can be used to detect mutations in these genes, serving to confirm the diagnosis and supply essential information for genetic counseling (Scheffer et al., 2017). This valuable diagnostic tool not only aids in the identification of de novo or inherited mutations but also provides insights into recurrence risks for affected families, helping to guide clinical management and intervention strategies (Scheffer et al., 2017).

In summary, the diagnosis of Doose syndrome relies on a combination of clinical presentation, EEG findings, and genetic testing. A multidisciplinary approach involving pediatric neurologists, genetic counselors, and other healthcare professionals can help ensure a comprehensive and accurate evaluation of patients suspected of having Doose syndrome. Early diagnosis and appropriate management are crucial for optimizing long-term outcomes and minimizing the impact of the condition on the patient's quality of life.
Table 1: Key Genes Associated with Doose Syndrome: Functions and Pathways

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function/Pathway</th>
<th>Reference</th>
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<tbody>
<tr>
<td>CHD2</td>
<td>Chromatin remodeling, regulation of gene expression, and DNA repair</td>
<td>(Trivisano et al., 2015)</td>
</tr>
<tr>
<td>SCN1A</td>
<td>Voltage-gated sodium channel function, action potential initiation and propagation in neurons</td>
<td>(Yordanova et al., 2011)</td>
</tr>
<tr>
<td>SLC6A1</td>
<td>GABA neurotransmitter transport, GABA reuptake from synaptic cleft</td>
<td>(Palmer et al., 2016)</td>
</tr>
<tr>
<td>STX1B</td>
<td>SNARE complex formation, synaptic vesicle fusion, and neurotransmitter release</td>
<td>(Vlaskamp et al., 2016)</td>
</tr>
<tr>
<td>GABRG2</td>
<td>GABA(A) receptor function, synaptic inhibition</td>
<td>(Oguni, 2022)</td>
</tr>
<tr>
<td>KCNA2</td>
<td>Voltage-gated potassium channel function, regulation of neuronal excitability</td>
<td>(Liu et al., 2018)</td>
</tr>
<tr>
<td>KCNB1</td>
<td>Voltage-gated potassium channel function, regulation of neuronal excitability</td>
<td>(Zavala-Yoe et al., 2016)</td>
</tr>
<tr>
<td>KDM5B</td>
<td>Histone demethylation, regulation of gene expression</td>
<td>(Nieto Barrera et al., 2003)</td>
</tr>
<tr>
<td>AP2M1</td>
<td>Clathrin-mediated endocytosis</td>
<td>(Helbig et al., 2019)</td>
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Treatment

The primary goal in treating Doose syndrome is to achieve optimal seizure control while minimizing the impact on cognitive and behavioral functioning. Various treatment options are available, which can be tailored to the individual needs of the patient. The following sections provide a detailed overview of the available treatments for Doose syndrome. However, the efficacy of these medications can be inconsistent, with some children achieving satisfactory seizure control while others persistently endure frequent seizures despite medicinal intervention (Zavala-Yoe et al., 2016). Consequently, supplementary treatment approaches, including dietary therapy—specifically, the ketogenic diet—may warrant consideration for enhanced seizure management (Dubru et al., 2002).

- Antiepileptic Drugs (AEDs)

AEDs are the first line of treatment for patients with Doose syndrome. The most commonly prescribed AEDs include valproate, lamotrigine, and topiramate (Doege et al., 2013; Press et al., 2015). These medications work by targeting different aspects of neuronal excitability, such as ion channels and synaptic transmission, to help reduce seizure frequency and severity.

- Dietary Therapies

Dietary therapies, such as the ketogenic diet and its variants, including the modified Atkins diet, have shown significant efficacy in reducing seizure frequency and severity in patients with Doose syndrome (Simard-Tremblay et al., 2015; Stenger et al., 2017; Wiemer-Krueel et al., 2017). These diets are high in fat and low in carbohydrates, which help to promote ketone body production. Ketone bodies have been suggested to have anticonvulsant properties that aid in seizure control.
• Immumomodulatory Therapies

For patients who do not respond well to AEDs or dietary therapies, immunomodulatory treatments, such as corticosteroids, may be considered (You et al., 2008). These medications work by suppressing the immune system and reducing inflammation, which may contribute to reduce seizure activity in some patients with Doose syndrome.

• Vagus Nerve Stimulation (VNS)

VNS is a neurostimulation therapy that has been shown to be effective in reducing seizure frequency in some patients with Doose syndrome (Nickels et al., 2018). The treatment involves the implantation of a device that sends electrical impulses to the vagus nerve, which is thought to modulate seizure activity by affecting various neurotransmitter systems in the brain.

• Corpus Callosotomy

In rare cases, when other treatment options have not been successful in controlling seizures, a surgical procedure called corpus callosotomy may be considered (Kanai et al., 2017). This procedure involves severing the corpus callosum, the large band of nerve fibers that connects the two hemispheres of the brain. By disrupting the communication between the hemispheres, this surgery aims to reduce the spread of seizure activity and improve seizure control.

• Highly Purified Cannabidiol

The use of highly purified cannabidiol (CBD) has emerged as a potential treatment option for various forms of epilepsy, including Doose syndrome (Devinsky et al., 2016; Szaflarski et al., 2018). CBD is a non-psychoactive compound derived from the Cannabis plant, which has shown anticonvulsant properties in preclinical studies and clinical trials (Klotz et al., 2018). Evidence suggests that CBD may exert its anticonvulsant effects through interactions with multiple molecular targets, including ion channels, neurotransmitter systems, and inflammatory pathways (Mechoulam and Hanuš, 2002). Although further research is needed to establish its safety and efficacy in Doose syndrome, initial reports indicate that CBD may offer a promising alternative or adjunctive treatment for patients who do not respond to conventional therapies.

It is crucial to work closely with a healthcare team experienced in treating Doose syndrome to develop an individualized treatment plan that addresses the unique needs of each patient. Treatment efficacy can vary from person to person, and adjustments may be necessary over time to maintain optimal seizure control and minimize any adverse effects on cognitive and behavioral functioning.

Prognosis

The prognosis of Doose syndrome, also known as myoclonic-astatic epilepsy, is quite variable and depends on several factors. Some children diagnosed with this condition can achieve complete seizure control and normal cognitive development, while others may continue to experience refractory seizures and cognitive decline (Stephani, 2006).

Factors associated with a poorer prognosis in Doose syndrome include:

1. Early onset: Children who experience the onset of seizures at a younger age are more likely to have a poorer prognosis. This may be due to the vulnerability of the developing brain to seizure activity and its potential
impact on cognitive and behavioral development (Inoue et al., 2014).

2. Presence of tonic seizures: The occurrence of tonic seizures in addition to myoclonic-astatic seizures may indicate a more severe form of the disorder, leading to a worse prognosis (Inoue et al., 2014).

3. High frequency of seizures at onset: A higher frequency of seizures at the beginning of the disorder has been correlated with a poorer prognosis. This may occur because frequent seizures can disrupt normal brain function and lead to long-term cognitive and behavioral impairments (Inoue et al., 2014).

To improve the long-term outcomes for children with Doose syndrome, it is crucial to initiate treatment as early as possible. Treatment options include:

1. Antiepileptic drugs (AEDs): AEDs, such as valproate, lamotrigine, and levetiracetam, are often the first line of treatment for Doose syndrome. These medications aim to control seizures and minimize their impact on the child's cognitive and behavioral development (Stenger et al., 2017).

2. Dietary therapies: Ketogenic diets and other dietary interventions, such as the modified Atkins diet, have been shown to be effective in controlling seizures in some children with Doose syndrome. These diets alter the body's metabolism by promoting the use of ketone bodies as the primary energy source, which may help reduce seizure frequency and improve overall prognosis (Nickels et al., 2018).

3. Comprehensive care: In addition to pharmacological and dietary interventions, a comprehensive care plan, including regular medical check-ups, ongoing monitoring of seizure activity, and access to educational and psychological support services, can help optimize the child's quality of life and long-term outcomes.

In conclusion, the prognosis of Doose syndrome is variable and depends on multiple factors. Early initiation of appropriate treatments, including AEDs and dietary therapies, can significantly improve long-term outcomes for children with this condition.

**Conclusion**

In summary, Doose syndrome, or myoclonic-astatic epilepsy (MAE), is a rare and complex childhood epileptic encephalopathy characterized by myoclonic-atonic seizures, generalized tonic-clonic seizures, and atypical absence seizures. The etiology of Doose syndrome is heterogeneous, with both genetic and environmental factors contributing to the disease. Despite advancements in understanding the genetic underpinnings, no major genetic factor has been identified, necessitating further research in this area.

Diagnosis of Doose syndrome relies on careful clinical evaluation, electroencephalographic findings, and, in some cases, genetic testing. Early identification of the syndrome is essential, as certain antiepileptic drugs may aggravate the condition, while others may provide better seizure control. Treatment options include medications such as valproate, levetiracetam, and lamotrigine, ketogenic and modified Atkins diets, corticosteroids, and, in refractory cases, corpus callosotomy. Recent studies exploring the use of highly purified cannabidiol for the treatment of refractory epilepsy also show promise for Doose syndrome.
Future research efforts should focus on elucidating the genetic and environmental factors involved in the development and progression of Doose syndrome, as well as identifying novel therapeutic targets. Additionally, further investigation of existing treatment options, including dietary therapies and highly purified cannabidiol, is necessary to optimize patient care and improve long-term prognosis for those affected by this rare and challenging epilepsy syndrome.

Conflicts of Interest:
Authors declare no conflicts of interest exist for this publication.

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References


