Genetic Mutations That Lead to Ohtahara Syndrome and Childhood Absence Epilepsy

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Abstract. Since epilepsy has become one of the biggest problems worried by the world, especially affecting thousands of children every year, many scholars have developed some therapies to try to save those families. One of the reasons why some people suffer from such illness is the genetic factors, which changes the function of the corresponding protein and causes a seizure. Among them, two representative diseases are Ohtahara syndrome and Childhood Absence Epilepsy. In the last century, as the mutated genes and the mechanisms of these two syndromes were still largely unknown, general antiepileptic drugs for them weren’t performing well in some conditions. Therefore, the demands for the mechanisms for these two diseases were increasingly higher though the complexity of human genes and genetic mutation still remains a challenging problem to the current technology. Luckily, extensive preclinical studies have shown that new drugs have promising therapeutic effects on these two syndromes. This article introduces the therapies for Ohtahara syndrome and Childhood Absence Epilepsy. There are going to collect the factors resulting from Childhood Absence Epilepsy and Ohtahara syndrome. Concluding past treatments and comparing them with the new therapies to find the medical progress in these two illnesses and whether Allopregnanolone, antisense oligonucleotides (ASOs) can help to treat Ohtahara syndrome, Zonisamide (ZSN), Levetiracetam (LEV), Topiramate (TPM) can treat Therapy-Resistant CAE.

Keywords: De novo SCN8A Mutation, Antisense Oligonucleotide, PCDH19 Mutation, Ganaxolone, Childhood Absence Epilepsy, Ohtahara syndrome, GABAA receptor, LVA calcium channels.

1. Introduction

Epilepsy is a central nervous system disorder caused by sudden abnormal discharge inside the brain. It may normally induce several symptoms such as temporary confusion, uncontrollable jerking movement of the arms and legs, and sometimes loss of consciousness and awareness. There are 9-10 million epileptics in China which is about 0.7% of the population, incidence and mortality rate of epilepsy in China is about 400 thousand per year and 30-80 thousand per year respectively. Epilepsy can be seen in all age groups and is the second most common encephalopathy in China which is only behind headache.

However, epilepsy is only the general term for this mental disorder. It includes several syndromes such as idiopathic epilepsy syndrome, benign epilepsy syndrome, and epileptic encephalopathy which are difficult to give an exact diagnosis. Besides, it is worth noting that the prevalence of epilepsy in children under 12 is significantly high than in other age groups which occupy 2/3 of the epileptics in China. The most persuasive explanation is that the genetic and structural factors are more likely to show during childhood. Nevertheless, the syndromes typically found in children and how these genetic mutations contribute to these syndromes still remain largely unknown. Recent studies have found several genetic mutations with their most convincing neuronal mechanisms which are responsible for different types of epilepsies.

This review specifically focuses on two typical syndromes found in children under 12 years old and summarizes potential genes and genetic mutations which may contribute to these syndromes. It also aims to introduce precise mechanisms of genetic mutations and to access possible treatments for each discussed syndrome.
2. The Ohtahara syndrome:

Ohtahara syndrome, also known as Early Infantile Epileptic Encephalopathy is classified as partial seizure and the symptom normally varies from moderate to severe. The mean age of seizure onset is normally from 4 to 5 months and the general range for onset is from birth to 18 months [1]. Children with Ohtahara syndrome are suffering from remarkable developmental impairment and mild to severe intellectual impairment. Besides many children with this syndrome have significant language disorders, they never talk or talk only when necessary; half of them cannot walk properly and others who can be able to walk will also suffer from incoordination, spasticity, or even loss the walking ability with developmental regression [2].

Since the exact mechanism and site of genetic mutations of Ohtahara syndrome haven’t been discovered in the early years, doctors can only use generic antiepileptic drugs (AED) to treat it, however, some of these AEDs such as Levetiracetam (LEV) is significantly related to psychiatric side effects such as depression and suicidal ideation as well as behavioral side effects such as irritability and emotional lability. This forced the patients to reduce the dose or even stop taking (LEW) though it has a good therapeutic effect [3]. Besides, as some of them are not specific to this syndrome, these drug treatments aren’t effective enough compare to targeted drugs. Nevertheless, recent studies have found two typical genes which play an important role in the development of Ohtahara syndrome. Although part of the mechanisms is still hypothetical, they indeed give a new way of thinking about treating this disorder.

2.1. The SCN8A gene and the antisense oligonucleotides (ASOs) therapy

The SCN8A gene is located on chromosome 12q13.13, which codes for a subunit of the voltage-gated ion channels Nav1.6 which is located at neuron axons, either in the nodes of Ranvier of the initial segments. Thus, it is crucial for controlling the depolarization of action potential and nerve conducting velocity [4]. Its structure consists of four protein domains and each domain contains six segments. For each domain, the fifth and sixth segments are used for the formation of hydrophilic ions pores and the fourth segment has a high sensitivity for the voltage change and is responsible for the membrane potential change during depolarization. There are two intracellular loops that connect domains 1-3 whereas domains 3 and 4 are connected by an inactivation gate.

The Ohtahara syndrome caused by SCN8A is an unusual dominant genetic disease called de novo heterozygous missense mutation [2]. It occurs when ovum and sperm from two parents with homozygous recessive genes fertilize, although the fertilized zygote should be supposed to be homozygous recessive, since there is a missense mutation during fertilization, the resultant zygote contains a dominant allele which will eventually cause an Ohtahara syndrome phenotype.

This will lead to missense mutations that will cause a gain of function mutation variants in highly conserved protein regions that are critical for Nav1.6 function such as the four domains and the inactivation gate between domains 3 and 4. As the amino acids in the highly conserved region have been changed, this will result in a change of protein tertiary and quaternary structure which will cause neuronal hyperexcitability that normally presents as a dramatic increase in consistent sodium current and an increased firing frequency [5]. These can be proved by a great hyperpolarization shift to the left in the Boltzmann function [6].

Since the cause of SCN8A encephalopathy has been identified as a gain of function variants that act on voltage-gated sodium ion channels, typical and specific drugs that act as sodium ion channel blockers such as carbamazepine, oxcarbazepine and phenytoin were applied soon after the SCN8A mechanism was found [2]. However, to minimize the side effect of treatment [1], a new genetic therapy called antisense oligonucleotides (ASOs) has soon been established. It's a molecule called gapmer which consists of 20 modified single-strand DNA nucleotides with a modified phosphate group and a 2′-O-methoxy-ethyl (2′-MOE) group at C3 of ribose which provide resistance to enzyme digestion as it enters the target mutated cell. As the gapmer molecule bind with the target SCN8A mRNA to form an RNA/DNA hybrid double strand, RNaseH1 will bind with it follows by forming an enzyme-substrate complex which cleaves the phosphodiester bonds of this hybrid thus destroying
the target SCN8A mRNA and prohibiting the expression of the gene [7]. It's worth noting that recent studies have already shown there is a dose-dependent reduction of SCN8A mRNA acquired in ASO-treated mutant mice when they were treated with 15 to 45ug of SCN8A gapmers on postnatal day 2 (P2). For mutant mice, their life spans will be extended to 9 weeks after receiving two injections at P2 and P30 separately which is 3 and 7 weeks longer than mutant mice with only one injection at P2 and untreated mutant controllers respectively. Besides, there is also a significant reduction of Nav1.6 on the brain neurons of ASO-treated mutant mice that are 3 weeks old [8]. Therefore, this will probably be the future of Ohtahara syndrome therapy caused by SCN8A.

2.2. The PCDH19 gene and Ganaloxone therapy

The *PCDH19* gene is a sex-linkage gene located on chromosome Xq22.1. It codes for the PCDH19 protein which is a member of the sigma-protocadherins subgroup. This specific protocadherin contains intracellular and extracellular domains which play different roles in the neuron synapse but both of their mutations will give rise to Ohtahara syndrome [9].

The intracellular part of PCDH19 is mainly coded by exon 2-6; it's responsible for the expression of the GABA-A receptor on the surface membrane and the control of GABA-A receptor intracellular transport as it binds to the alpha subunit of the ligand-gated channel protein [10]. GABA-A receptor normally serves as the receptor of the inhibitory neurotransmitter gamma-aminobutyric acid, which is the major inhibitory neurotransmitter in the brain. It mediates the facilitated diffusion of negative chloride ions which hyperpolarize the neuron to control the firing frequency of action potential. Therefore, the intracellular part of PCDH19 is crucial as it can be able to control the number of GABA-A protein channels located on the postsynaptic membrane.

The extracellular part of PCDH19 is coded by exon 1 and most of the disease-causing mutation is located at this part. The ectodomain consists of 6 identical extracellular cadherins (EC) repeats. These six ECs will interact with the ECs on the surface membrane of other neurons in synapses in trans and with Ncad from the same cell in cis. Both of these adhesion processes are responsible for cell migration and circuit formation [9].

The Mutation of both intracellular and extracellular domain code by *PCDH19* gene is significant for the development of Ohtahara syndrome.

For the intracellular domain, the altered 3D shape may probably no longer bind to the alpha subunit as usual which will influence the surface expression of the GABA-A receptor which will lead to Ohtahara syndrome as less Cl- will enter the postsynaptic element through GABA-A ligand-gated channels to decrease the membrane voltage potential. Moreover, it is worth noting that recent studies also found that PCDH19 patients may also have a lower level of allopregnanolone compared to normal people [11]. It has been identified that allopregnanolone is a neurosteroid that derives from the female hormone 5-alpha-dihydroprogesterone and what it does is act as a positive allosteric modulator of GABA-A receptor though where allopregnanolone is formed inside the body is still unknown. Some scientists have discovered a reduced level of skin fibroblast enzyme AKR1C3 will result in a reduced amount of allopregnanolone in the blood. Thus, they supposed the allopregnanolone was firstly converted inside the fibroblasts and was then transported into the brain through the blood-brain barrier (BBB) followed by typical modulation inside the brain to convert 5-alpha-dihydroprogesterone into allopregnanolone [11, 12]. Since positive allosteric modulator can cause a conformational change of GABA-A receptor which leads to an increase of affinity for the orthosteric site to the ligands such as neurotransmitter GABA as well as the ability to induce an intracellular response, thus a decreased amount of allopregnanolone will lead to dysfunction of GABA-A receptor in patients' central nervous system which causes the increased firing of action potentials [12].

For the extracellular domain which is far more complicated, it only affects female patients with heterozygous *PCDH19* allele on the sex-linkage chromosome. The animal models have shown that there is a decrease in the size of postsynaptic elements and a loss of vesicles in mossy fibrous synapses in cone neuron CA3 in female mice with heterozygous *PCDH19* allele while wild type female mice
do not contain this phenomenon. Thus, scientists affirm this abnormal mutation is similar to the principle of tortoiseshell cat's fur. As the PCDH19 gene is only presented on the X chromosome, the male only has one of it while the female has two of them, therefore to ensure an appropriate gene expression level as male, the female needs to random inactivate one of the alleles on two X chromosomes which will result in a random presence of PCDH19 cadherin on the surface of neurons [13]. Based on this mechanism, two hypotheses of cell interference have been established. Since the neurons recognize each other through a specific "chemoaffinity label" [9, 13], the first one claims that the loss of PCDH19 protein may cause premature development and increased neurogenesis of the neurons. Different timing of growth of neurons will lead to abnormal cell-to-cell interaction as they have different chemoaffinity labels. This will then lead to a failure of network formation follows by Ohtahara syndrome as the maturity of the cell is important in the connection of cadherins [14].

The second one supposes that the wild-type female N-cadherin and PCDH19 cadherin will form a dimer that interacts with the same dimer from the postsynaptic element which promotes presynaptic signaling and development mediated by B-catenin. This signal transduction pathway is crucial in cell migration and synapse formation [9, 15]. However, as the heterozygous PCDH19 female contains some neurons which do not contain PCDH19 cadherin due to random inactivation, besides, since chemoaffinity labels between N-cadherin and PCDH19 cadherin are different, these neurons cannot form a signal transduction pathway at the synaptic cleft as usual which will result in abnormal cell migration, synapse formation together with decrease number of vesicle and neurotransmitter form (e.g. GABA) [13]. These series of changes will eventually cause the symptoms of Ohtahara syndrome. What's more, it is worth noting that recent studies have found that mosaic males will also have Ohtahara syndrome. Although the normal male is hemizygous and neurons either form a connection with other cells using dimer as usual or only using N-cadherin when the allele on the X chromosome is recessive [13], scientists have noticed five mosaic males who have two different types of hemizygous cells in the bodies which contain or do not contain PCDH19 cadherin separately and their percentage varies from 20% to 78% in their blood samples [16]. Therefore, mosaicism will cause these males to have a similar phenomenon as heterozygous females. However, as mosaic male samples have just been discovered, the exact mechanism and the cause of mosaicism still need to be explored and detected.

In previous years, the special treatment for PCDH19 mutation was still unsure. Anticonvulsant drugs and corticosteroid treatment were used to relieve the seizure however the relief is transient and seizures will reoccur in most the patients [16]. With the help of the discovery of allopregnanolone and its function, a synthetic drug called ganaloxone which is similar in structure to allopregnanolone has been invented and applied for treatment. A phase 2 study of ganaloxone has shown that the median change in seizure among 11 PCDH19 mutant patients over 28 days was 26% lower, furthermore 6 out of 11 these patients had a significantly greater reduction of seizure compared to the mutant controllers [15]. Besides a test in children also has shown this drug was exceptionally safe with its most remarkable side effect being somnolence. A recent study even shows that ganaloxone is even more efficient than natural allopregnanolone using mouse models [12]. Therefore, ganaloxone treatment will probably be the future of Ohtahara syndrome therapy caused by PCDH19 mutation.

Besides, recent studies have also found other mutations which will lead to Ohtahara syndrome such as the mutated KCN2 gene will contribute to the formation of voltage-gated potassium ion channels [17], and CYFIP1 and 2 which contribute to regulating mRNA translation, actin polymerization, and exceptional activation of Wave regulatory complex [18]. Although their mechanisms are still not completely certain, with the development of DNA sequence determination technology and more experiments on animal modes, we will soon understand the exact mechanisms of these mutations and develop specific drugs or even genetic therapy such as ASO to treat them.
3. Childhood Absence Epilepsy

As a common pediatric generalized epileptic syndrome, children absence epilepsy (CAE) has been diagnosed all over the world and affects 10-17% of children with epilepsy. When CAE occurs, it always causes a multiple absence seizure and ends abruptly [19].

Although most the studies on CAE haven’t pointed out its genetic pathways to improve its precision therapies, the newest research has tried to improve disease risk predictability by locating the genetic variants associated with CAE. Especially, most the mutation would affect the ion channel (calcium channel, GABA receptor) [20]. In addition, some investigations in CAE also illustrate the channel genes CACNA1H, CACNA1G, CACNG3, along with two mutations in gamma-aminobutyric acid receptor subunit gamma-2, are associated with a CAE-like phenotype. Since affecting the ion channel may cause CAE, in the last ten years, many scholars have carried out various studies to find out some useful treatment strategies for CAE.

3.1. LVA calcium channels

CACNA1G(Cav3.1), CACNA1H(Cav3.2), and CACNA1I are three gene coding variants that impact calcium channels (Cav3.3). CACNA1G is found on 17Q21.33 and is mostly expressed in the thalamocortical neurons where the spike-wave discharges occur. In the intracellular region of the protein within the i-II ring, this mutation results in an amino acid exchange between alanine and valine at position 570[21]. In addition, other variants may influence the alternative splicing of genes, so there are at least five different subtypes with different kinetic and homeostasis characteristics in the Cav3.1 channel [22]. CACNA1G was shown to be overexpressed in mice with low and high transgene copy numbers in a study. This causes an increase in α1G expression, which leads to an increase in functional T-mode current in thalamic neurons. Both transgenic lines displayed SWD, although seizure frequency did not differ significantly. Furthermore, the mice showed no other neurological disorders, indicating that the increase in Cav3.1 caused pure absence seizures.

CACNA1H gene (Cav3.2) is located on chromosome 16p13 3, expressed in the thalamic reticular nucleus [23]. It is widely alternatively spliced and produces a family of variant transcripts [24]. Different variants change the gated voltage domain, activation, deactivation, and deactivation recovery dynamics, as well as the voltage midpoint and the size of the function window current. Therefore, changes affecting the splicing of ESE regulatory sites or intron regions in exons may induce seizures. T-type channel activity was found to increase due to changes in activation potential in all mutants. The channel is activated in response to small voltage changes, or changes in the rate at which the channel recovers from the inactivated state (inactivation), or an increase in channel surface expression.

A study in another group of the Chinese population further confirmed the possible role of CACNA1H in the absence epilepsy, in which five exon variants (p314s, n345n, p492s, l602l and s619s) and nine rare intron variants were found [25]. Therefore, it is predicted that exon variation will change the secondary structure of transcriptional binding, splicing sites, or channels, but the results found that a common variation in intron 11 (rs2745150) is highly correlated with CAE and is considered that it may change the potential splicing sites. In the model of multigene deletion epileptic rats (GAERS), a mutation was found in exon 24, resulting in arg158pro. Further studies showed that CACNA1H had two splice variants in the thalamus, one with exon 25 and the other without. During high-frequency bursts, the mutation resulted in significant and rapid recovery of channel inactivation and greater Ca2 + influx, but only when it occurred on the variation with exon 25 [21]. In addition, in human studies, it was found to be located on chromosome 16p13 on 1-p12 γ. The 3-subunit gene (cacng3) is associated with CAE in European populations: it confirms the unique role of regulatory subunits in channel function, leading to seizures.

The CACNA1I gene is found on chromosome 22q13.1 and is expressed mostly in the thalamic reticular nucleus [23]. However, no mutations were found in Chinese CAE patients when a mutational investigation was performed. The CACNA1I gene is found on chromosome 22q13 and is mostly expressed in the thalamic reticular nucleus. It can regulate the function, assembly, and positioning of
the channel. It is a non-pore-forming regulatory subunit of the Ca2+ channel and may also be a candidate unit for burst ignition [26]. β4 Subunit can be combined with α1A (type P/Q) and α1B (n-type) subunit interaction. In the animal model of epilepsy (sleepy mice), β A mutation found in the 4-subunit gene (cacna1b) showed seizures and ataxia. This mutation leads to the truncation of one cytoplasmic protein and may lead to other mutations β Subunits and α Subunits are assembled together to compensate for mutations at hippocampal synapses. However, thalamus β Subunit 4 is highly expressed, while β 1- β 3 subunit is not highly expressed; This suggests that there may not be a compensatory mechanism of inhibitory function in the thalamus, so the mutation may lead to slow-wave discharge.

3.2. GABAA receptor

γ-aminobutyric acid type A (GABAA) receptor is a member of the Cys-loop superfamily of ligand-gated ion channels [27], which is the main mediator of central nervous system inhibition. The receptor consists of five subunits arranged in a ring enclosing a central chloride channel. The most numerous subunits are α1, β2, and γ2, which form counterclockwise receptors for β2α1γ2β2α1, as seen from the synapse. The binding of GABA at the β2 and α1 subunit interfaces triggers channel opening [28]. So, when one of the subunits in the γ-aminobutyric acid type A (GABAA) receptor changes, it may cause discharge.

Furthermore, three CAE-associated mutations in GABAA receptor 3 subunits have recently been identified: GABRB3(P11S), GABRB3(S15F), and GABRB3(G32R) [29]. Current density was lowered in mutant subunit-containing receptors. Besides, except digested with an enzyme that eliminated all N-glycans, the mutant proteins seemed to be "hyperglycosylated," as they migrated at greater molecular masses than wild-type β3 subunits. As a result, the researchers believed that 10.5 hyperglycosylated might cause lower current density, which might contribute to neuronal hyperexcitability and, eventually, aberrant EEG patterns in the absence seizures.

Although Katharine N. Gurba observed variation inflicted by the G32R mutation that lowered mutant receptor function, it was recently established that tonic GABAergic current is paradoxically aggrandized in thalamocortical neurons from two rat models of absence epilepsy [30]. This suggests that the G32R mutation promotes hyperexcitability predominantly via cortical and/or postsynaptic GABAA receptors. If this is the case, it could explain why this mutation is linked to children absence epilepsy, as cortical 3 subunit expression decreases when children grow up, as cortical 3 subunit expression decreases throughout development. As a result, GABAA deficiency could be a factor.

3.3. Therapy

3.3.1. Ethosuximide

As the first choice for CAE in a simple absence seizures condition, Ethosuximide won’t affect focal and generalized tonic-clonic seizures [31]. Instead, it temporarily blocks the thalamus’s low-threshold calcium currents. It is vital to note whether it would impact the effects of enzyme-inducing and inhibiting antiepileptic medicines when used in combination with various oral formulations (syrup, capsules) [32]. By inhibiting the brief and low threshold calcium current created by T-type calcium channels in thalamic neurons, ESX blocks the synchronized discharge of cortical thalamic neurons, which causes the spike-wave discharge of absence seizures.

3.3.2. Valproic Acid

As a broad-spectrum antiepileptic drug is working on both pre and post-synaptic, besides, VPA has a variety of mechanisms [31], including increasing the level of gamma-aminobutyric acid (GABA) in the brain, blocking voltage-sensitive sodium channels, and activating calcium-dependent potassium conductance, so it can help to inhibit GABAergic over glutamatergic transmission and regulate the ionic currents.
3.3.3. Lamotrigine

Lamotrigine can increase the stability of presynaptic membranes and limit its neurotransmitters effect by inhibiting neurotransmitters release, especially glutamate and aspartate [31]. So, the mechanism of Lamotrigine is blocking the voltage-dependent sodium channels to control the illness. However, there also have some patients who can’t be cured by these three drugs, because there is a further variation Therapy-Resistant CAE. So here are some drugs that have been used to treat it.

3.3.4. Levetiracetam (LEV)

LEV was designed to be used as monotherapy or as adjunctive therapy to treat various generalized epilepsies and also used to treat Therapy-Resistant CAE. LEV can not only affect the a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor channels, but also won’t affect glutamate or GABA-mediated synaptic transmission and modulation of voltage-dependent sodium or T-type calcium currents by blinding to SV2A synaptic vesicle glycoprotein [33]. As for now, it has been shown that LEV has a great curative effect on those patients who suffer from the Therapy-Resistant CAE.

In an open-label study, LEV (1–2 gr/day; maximum dose 70 mg/kg/day) was tested for effectiveness, tolerability, and safety in children with CAE as a single monotherapy [34]. Eleven of the twenty-one participants recovered from their seizures, and one experienced a greater than 50% reduction in symptom severity, proving that LEV was safe and had no side effects during the study.

3.3.5. Topiramate (TPM)

Topiramate (TPM) is a sulfamate modified fructose diacetonide molecule that can increase the inhibitory impact of GABA while also inhibiting the excitatory glutamate pathway. Furthermore, it inhibits carbonic anhydrase activity and blocks voltage-dependent sodium and calcium channels. Cross et al. (2002) [35] tested the therapeutic utility of TPM in five children with TAs on 24-hour ambulatory EEG in an open-label, single-site pilot experiment. The youngsters had previously been untreated or had failed to respond to other ASMs [33]. After six weeks, ambulatory EEG monitoring was used to assess response. As a result of the study, one previously untreated child became seizure-free, two patients got seizure reductions, and the remaining patients received no benefit. No child withdrew due to adverse effects. This also proves that TPM was safe in this trial with no negative effects.

3.3.6. Zonisamide (ZSN)

By inhibiting carbonic anhydrase and blocking T-type calcium channels as well as voltage-sensitive sodium channels, zonisamide (ZSN) is thought to impede sustained, repetitive neuronal activity [33]. Wilfong et al. [36] studied the safety and efficacy of ZNS in 45 patients aged 18 years with absence seizures, despite the fact that there are minimal of data on its use. Seizure freedom was attained in 23 (51.1%) of these individuals. Two individuals have stopped using ZNS because their seizures have gotten worse or they are experiencing negative effects (sedation)
Table 1. The summary of therapies for resistant CAE

| Therapies for resistant CAE | Efficacy and characteristics                                                                 | Side effect                                                                 |
|-----------------------------|-----------------------------------------------------------------------------------------------|-------------------------------|
| **Older therapeutic options** |                                                                                               |                               |
| Ethosuximide                | Blocking the transient and low threshold calcium current produced by T-type calcium channel in thalamic neurons | Ataxia, [37] fatigue, irritability, dizziness, anorexia, cramps, diarrhea, and abdominal pain |
| Valproic Acid               | Increase the level of gamma-aminobutyric acid (GABA) in the brain, block voltage-sensitive sodium channels, and activate calcium-dependent potassium conductance | Weight gain, tremor, and [37] gastrointestinal symptoms                     |
| Lamotrigine                 | Sodium channel blocker                                                                      | Nausea, weakness, headache, [37] anxiety, insomnia, and irritability          |
| Clonazepam (CLN)            | It inhibits synaptic transmission throughout the central nervous system by binding to the benzodiazepine site of the GABA receptor and causing chloride ions to enter into neurons. | Lack of concentration, [37] sedation, and ataxia                             |
| **New therapeutic options** |                                                                                               |                               |
| Topiramate                  | Block sodium and calcium channels that are voltage-dependent. It can also inhibit the excitatory glutamate pathway, increase the inhibitory impact of GABA, and inhibit the activity of carbonic anhydrase. | Drowsiness, [37] anorexia, fatigue, and irritability                          |
| Levetiracetam               | Inhibition of presynaptic calcium channels                                                   | Drowsiness, [37] weakness, dizziness, and irritability                        |
| Zonisamide                  | Blocking voltage-sensitive sodium and reducing voltage-sensitive T-type calcium channels to block sustained and repeated neuronal discharges, so as to play an anticonvulsant role | Sedation                                                                 |

4. Conclusion

In the last decades, as the mutated genes and the mechanisms of these two syndromes were still largely unknown, general antiepileptic drugs for them weren’t very effective and often along with undesirable side effects such as vomiting and sleepiness. With the help of improved sequencing techniques such as next generation sequencing, the sites of the genetic mutations which cause abnormal functions of the proteins can be identified. This automatically leads to better-targeted therapies for Ohtahara syndrome such as the ASO gapmer and the ganaloxone which are specifically designed for SCN8A mutation and PCDH19 mutation respectively. Both of them have already shown they have a much more efficient therapeutic effect together with minimized side effects. Nevertheless, this does not mean that scientists have already overcome these two diseases; several fundamental issues still have to be solved. For example, gapmer molecules for treating SCN8A Ohtahara syndrome have a relatively short half-life. How to elongate the half-life of gapmer molecules in order to
eliminate the tedious journey between hospitals and patients’ homes? Besides the TPM and ZNS for treating childhood absence epilepsy still have non-negligible drug resistance, how to successfully treat the seizure without developing the resistance? The most possible answer to these questions is a much more mature genetic therapy. Furthermore, CRISPR/Cas9 technology has also been discovered in recent years, it’s also possible to predict that gene therapy will become the future development direction for therapy of both Ohtahara syndrome and childhood absence epilepsy.

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