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Women With Genetic Epilepsies

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Abstract

Some epilepsy syndromes are more common in female individuals. Often, these syndromes have an underlying genetic variant involving the X chromosome that is typically lethal in male individuals, resulting in a higher female prevalence. However, some of the idiopathic generalized epilepsies such as juvenile myoclonic epilepsy are conditions with complex inheritance, with thousands of variants in genes throughout the genome. But they can also have a predominance in female individuals. In this study, we performed a narrative review of PubMed and Scopus using the following entries: "epilepsy in women," "genetic epilepsy in female individuals," "epilepsy genetics in women," "female-specific epilepsy genetics," "epilepsy and genetic mutations in female individuals." The findings were synthesized and described according to clinical characteristics, underlying genetic mechanisms, and treatment considerations for these epilepsy syndromes manifesting largely in female individuals. The epilepsy syndromes reviewed here include Rett syndrome, *CDKL5* deficiency disorder, *PCDH19*-related epilepsy, subcortical band heterotopia, periventricular heterotopia, Aicardi syndrome, and juvenile myoclonic epilepsy. Recognizing these epilepsy syndromes and understanding their underlying genetic etiology helps provide a tailored treatment approach early in the course of the disease. It can also assist with genetic counselling for family members who plan to have children.

Introduction

Epilepsy is more prevalent in male individuals; however, some subtypes are known to be more common in female individuals. This sex difference is well established for some conditions such as in X-linked disorders, while it is not so well-understood for others such as juvenile myoclonic epilepsy (JME).[1] In this study, we explore this sex difference in genetically determined epilepsies.

Methods

In this narrative review, a literature search was conducted using PubMed and Scopus with the following search entries: "epilepsy in women," "genetic epilepsy in female individuals," "epilepsy genetics in women," "female-specific epilepsy genetics," "epilepsy and genetic mutations in female individuals." Publications in English language were selected, and the date range was set from 2014 to 2024. The resulting studies were selected based on title relevance.

Findings

Genetic epilepsies in female individuals encompass a heterogenous group of disorders, several of which are X-linked. Monogenic epilepsies most frequently affecting female patients include Rett syndrome, *CDKL5* deficiency disorder (CDD), and *PCDH19*-related epilepsy. Subcortical band heterotopia (SBH) and periventricular nodular heterotopia (PNH) can be caused by

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Glossary

AAV = adenoassociated virus; **AS** = Aicardi syndrome; **CDD** = CDKL5 deficiency disorder; **IGE** = idiopathic generalized epilepsies; **JME** = juvenile myoclonic epilepsy; **PNH** = periventricular nodular heterotopia; **RTT** = Rett syndrome; **SBH** = subcortical band heterotopia; **SBH** = subcortical band heterotopia; **XCI** = X-chromosome inactivation.

variants in several different genes. Aicardi syndrome may be monogenic, but its genetics have not yet been clarified. Another form of epilepsy which is more prevalent in female patients is JME, which has a complex genetic architecture, with several thousands of genetic variants of small effect playing a role in phenotype. To date, there is no specific treatment for these genetically determined epilepsies in female patients, although new treatments, including DNA/RNA-based ones, are being studied. Advances in molecular genetics research will lead to a better understanding of pathology, natural history of the disease, and hopefully tailored treatment in these conditions.

X-Linked Genetic Epilepsies in Female Individuals

Haploinsufficiency is a condition where 1 copy of the gene is mutated, and the remaining normal copy cannot produce enough protein to maintain normal function. Since male individuals have only 1 copy of the X-chromosome, a disease caused by an X-linked gene haploinsufficiency can be significantly more severe or even embryonically lethal.

Women have 2 copies of X chromosome, resulting in double the number of gene products. To compensate for this gene dosage imbalance, one of the X-chromosomes (maternal or paternal) is randomly inactivated during early embryonic stages (X-chromosome inactivation [XCI]).[2] XCI is an epigenetic mechanism not yet completely understood.[3] Furthermore, approximately 15%–30% of X-linked genes can escape this silencing mechanism and are expressed from both maternal and paternal copies of the gene.[2,e1] It is also unclear how the decision to silence the paternal or maternal chromosome is made, but when one of the parental X-chromosomes is silenced more often than the other, a "skewed XCI" pattern emerges. If an abnormal gene is on the parental X-chromosome that was mostly silenced, there will be a smaller amount of abnormal protein which may account to a less severe phenotype. The different patterns of XCI may explain, at least in part, why women with the same genetic variant can express variable phenotypic severity.

Examples of epilepsies due to X-linked genes haploinsufficiency include Rett syndrome, CDD, SBH, and PNH. *PCDH19*-related epilepsy has a different mechanism, where cells carrying normal and abnormal PCDH19 protein product interfere with each other, a mechanism called "cellular interference." Genetic counselling is important because once a female patient is diagnosed, her parents, herself, or adult siblings can be made aware of the risks for future pregnancies.

Rett Syndrome

Rett syndrome (RTT) is a multisystem neurodevelopmental disorder considered to be one of the most common causes of developmental and intellectual disability in female patients.[4] Its incidence is approximately 1:10,000–20,000.[4]

Typical RTT can be divided into 4 clinical stages: stage I (6–18 months): developmental arrest with hypotonia, delay in gross motor skills, loss of hand skills and speech, less eye contact, social interaction, and interest in toys. Stage II (18–36 months): rapid destructive with autistic features, intellectual disability, hand stereotypes, motor dysfunction, respiratory abnormalities, and microcephaly. Stage III (approximately 2–10 years): plateau with seizures, variable improvement in behavior, eye contact, and hand use. Stage IV (beyond 10 years): late motor deterioration with further motor deterioration, spasticity or dystonia, scoliosis, loss of the ability to walk (IVa), or never ambulant (IVb).[4] These 4 clinical stages can correlate with characteristic EEG findings (see Table 1 and the supplementary data, eAppendix 1).

Atypical Rett syndrome is characterized by some form of developmental regression, followed by stabilization (Table 1).[5] In addition, individuals must have at least 2 of the 4 main diagnostic criteria and 5 of the 11 supporting criteria for RTT.[5] The main diagnostic criteria include partial or complete loss of acquired purposeful hand skills, partial or complete loss of spoken language, gait abnormalities, and stereotypic hand movements. Supporting criteria include breathing disturbances while awake, bruxism while awake, impaired sleep, abnormal muscle tone, peripheral vasomotor disturbances, scoliosis or kyphosis, growth retardation, small cold hands and feet, inappropriate laughing or screaming spells, diminished response to pain, and intense eye communication. Some of the previously called "atypical Rett" conditions have been linked to other genes and are now considered different diseases (see below).

Rett Syndrome Genetics

MECP2 maps to chromosome Xq28 and encodes MeCP2, a methyl-CpG-binding protein.[6] *MECP2* acts as a transcriptional regulator, repressing or activating gene expression through its binding to methylated DNA of other genes. *MECP2* is also involved in chromatin remodeling, making other genes more or less accessible to transcription. *MECP2* also modulates synaptic plasticity, which is necessary for learning, memory, and overall cognitive function. Another role of *MECP2* is related to neuronal growth, structure, and

Table RTT Diagnostic Criteria 2020

RTT diagnostic criteria 2020
Consider diagnosis when postnatal deceleration of head growth observed
Required for typical or classic RTT
1. A period of regression followed by recovery or stabilization 2. Partial or complete loss of acquired purposeful hand skills 3. Partial or complete loss of spoken language 4. Gait abnormalities: impaired or absence of ability 5. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
Required for atypical RTT
1. A period of regression followed by recovery or stabilization 2. At least 2 of the 4 main criteria 3. Five of 11 supportive criteria 4. Breathing disturbances while awake 5. Bruxism while awake 6. Impaired sleep 7. Abnormal muscle tone 8. Peripheral vasomotor disturbances 9. Scoliosis/kyphosis 10. Growth retardation 11. Small cold hands and feet. 12. Inappropriate laughing/screaming spells 13. Diminished response to pain 14. Intense eye communication: 'eye pointing'

connectivity, including balancing between excitatory and inhibitory signals.[7]

Variants in the *MECP2* gene cause 95% of typical RTT cases and up to 73% of atypical RTT cases.[4] However, other genes such as *FOXG1* and *GRIN2B* have been associated with atypical cases.[8] Haploinsufficiency allows female individuals to survive. On the other hand, male individuals have only 1 copy of *MECP2*, and when this copy carries the pathogenic variant, all cells are equally affected. This leads to male embryo lethality or, if they are born, a more severe phenotype. Exceptions are cases of Klinefelter syndrome, where male individuals have 2 X chromosomes, or mosaics.[4] Genotype-phenotype correlations are not completely understood. Early truncations, large deletions, and some specific point variants are associated with more severe phenotypes.[4] While low levels of MeCP2 protein lead to Rett syndrome, overexpression of *MECP2* is also harmful. For instance, male individuals with *MECP2* duplication have a severe neurodevelopmental disorder, with ID, seizures, autism, hypotonia, and several other manifestations.[9]

Rett Syndrome Treatment

Recent studies have suggested that the efficacy of ASMs is age-dependent, where children aged less than 5 years may benefit from valproate (VPA) and patients 15 years or older benefit from carbamazepine.[10] New sodium channel blockers may be better options for epilepsy in Rett syndrome that were not explored in the literature. Clinicians may have preference for some medications over others due to behavioral side effects. For instance, the use of lamotrigine is often preferred over levetiracetam to avoid potential mood symptoms, agitation, and psychosis. In a longitudinal cohort study on the use of cannabidiol as an adjunctive therapy in combination with clobazam, the combination group reduced seizure frequency in 7 of the 10 patients, with 1 seizure-free patient, no adverse effects, and improvement in agitation, anxiety attacks, and spasticity.[11]

Recent studies in Mecp2 animal models have identified rational molecular targets for drug therapies, including neurotransmitter signaling, growth factor signaling, and metabolism.[7] BDNF is a mediator of neuronal and synaptic maturation, and is down-regulated with loss of functional MeCP2. Overexpression of BDNF has been shown to partially rescue the Mecp2 phenotype in null mice.[e2] However, studies in humans did not provide positive results. Trofinetide is a synthetic analog of glycine-proline-glutamate, the N-terminal tripeptide of the insulin-like growth factor 1 protein. A recently published phase 3 clinical trial found a statistically significant improvement in the "Rett Syndrome Behaviour Questionnaire" and the "Clinical Global Impression" scales with the use of trofinetide. This trial also demonstrated an acceptable safety profile.[12] A phase II clinical trial with oral ketamine is ongoing.[13]

Disease-modifying treatments such as gene therapy, X-chromosome reactivation, genome editing, and RNA editing have also been extensively studied, especially in animal models. A most recent (July 2024) phase 1/2 trial evaluating the results of adenoassociated virus (AAV)–based gene therapy for Rett syndrome in humans showed this treatment to be well-tolerated in the first 3 patients.[14] More patient data are needed to understand the role of AAV-therapy in this condition.

CDKL5 Deficiency Disorder

CDKL5 deficiency disorder (CDD) is a heterogeneous developmental and epileptic encephalopathy disease resulting from the nonfunctional or absent CDKL5 protein.[15] The prevalence of CDD is estimated at approximately 1 in 40,000–60,000 live births.[16] Patients with CDD were previously described as having atypical RTT; however, this condition can be clinically distinguished from RTT based on a much severe developmental delay from birth and seizure onset before the age of 3 months.[6] These infantile-onset refractory seizures may include infantile spasms (81% of the cases), tonic, myoclonic, tonic-clonic atypical absences, and focal seizures. These patients also have generalized hypotonia, intellectual disability, developmental delay, and cortical vision disorders.[15]

Compared with female patients with Rett syndrome, female patients with CDD are more likely to have seizures and sleep disturbances, while they are less likely to have breathing, spinal curvature, gastrointestinal problems, or hand stereotypies.[6]

CDKL5 Genetics

Patients with CDD, often have de novo variants in the *CDKL5* (cyclin-dependent kinase-like 5) gene. *CDKL5* belongs to the same molecular pathway as *MECP2*. *CKDL5* plays a

significant role in early brain development, neuron differentiation, and growth. It is also important in synaptic plasticity and neuronal signaling cascades.[e3] Pathogenic variants of *CDKL5* expressed in male embryos are usually lethal or lead to severe phenotypes, sometimes with premature mortality.[16] As with Rett syndrome, exceptions are cases of Klinefelter syndrome, or mosaics. Of interest, rare male individuals with RTT-like features have been shown to have *CDKL5* pathogenic variants.[17]

CDD Treatment

There is no specific ASM that is preferred in CDD treatment. Various ASMs have seen partial success: vigabatrin, lamotrigine, topiramate, clobazam, valproate, felbamate, and zonisamide.[18] However, the responder rate typically decreases overtime, with no statistically significant difference in response rates between infantile spasms and other seizure types.[19] Overall, seizure freedom is challenging to achieve in patients with CDD, and reduction in seizures has not been shown to exhibit improvement in cognitive functioning.[19]

Sodium channel blockers such as oxcarbazepine, carbamazepine, and lacosamide have demonstrated some effectiveness in younger patients with focal features and no history of West syndrome.[20] Cannabidiol, typically used in tandem with other treatments, has also demonstrated some efficacy in patients with CDD.[18]

Recent clinical trials have identified fenfluramine as a promising drug for reducing seizure frequency in CDD.[21] Other active trials have noted ganaxolone[22] and soticlestat[23] to be well-tolerated and effective for seizure reduction.

Patients with CDD may also need treatment for their sleep disturbances, behavioral dysregulation, and movement disorders.[18] Data on use of such treatments are limited. However, recent animal studies have shown that postdevelopmental restoration of *Cdkl5* expression in young adult mice is sufficient to ameliorate NMDAR-related synaptic deficits that reverse behavioral deficits in mice.[24] Forniceal deep brain stimulation in *Cdkl5* knockout mice also rescued hippocampal memory deficits, warranting further investigation toward the potential of DBS as a therapeutic option for CDD cognitive disturbances.[25]

Subcortical Band Heterotopia

Subcortical band heterotopia (SBH) also known as double cortex syndrome, is caused by pathogenic X-linked *DCX* variants producing a classic example of deficient neuronal migration-associated malformation.[26] Such heterozygous *DCX* variants in female individuals result in a spectrum of neurodevelopmental disorders. While female patients with *DCX* variants have SBH, male patients usually have classic lissencephaly.[26] In some cases, there is an overlap between lissencephaly and SBH, with SBH in occipital regions and pachygyria in frontal regions.[27] Rarely lissencephaly can also be associated with severe hypoplasia of the corpus callosum.[26]

Two distinct subgroups among female patients with *DCX* pathogenic variants have been proposed.[e4] The first is a more severe clinical phenotype, usually caused by de novo variants, presenting with refractory epilepsy and severe intellectual disability. The second is a milder phenotype mainly observed in heterozygous asymptomatic female individuals with normal cerebral MRI or only thin frontal subcortical bands, also majorly due to de novo variants.[e4]

Almost all patients with severe SBH have epilepsy, which is drug-resistant in 65%–78% of patients.[e4] More severe MRI abnormalities are associated with significantly earlier seizure onset, where individuals are more likely to develop Lennox-Gastaut syndrome.[26]

SBH Genetics

DCX pathogenic variants are seen in most cases of familial SBH and in 53%–84% of sporadic, diffuse, or anteriorly predominant band heterotopia cases.[28]

DCX regulates embryonic neuronal migration through its role in maintaining microtubules proper functioning. In female patients, the proposed mechanism for SBH formation is that neuronal migration occurs abnormally in the neurons carrying the abnormal *DCX* and it occurs normally in the neurons carrying the normal *DCX* variant. As such, depending on the random CXI pattern, a person can have a large or a small number of abnormal neurons forming the SBH. However, the type of variant is also important because some variants can lead to small, thin bands while others can lead to thick bands, independently of the CXI pattern.[e5]

Some female patients may have milder phenotypes, with mild intellectual disability with or without epilepsy, and normal MRIs.[e6] These female patients can have children affected with varying phenotypes of SBH and lissencephaly.[e6] Skewed X inactivation was observed in these carriers' lymphocytes. Although this same mechanism cannot be proven to occur in the brain, it might explain the heterogeneity in the female carriers. Rare cases of SBH in male individuals were seen in patients with somatic mosaicism, suggesting that somatic mosaicism in male individuals is the equivalent of random CXI in female individuals.[e7]

Although most cases of SBH are caused by *DCX*, other genes, which are not located on chromosome, X can also cause SBH, including, *LIS1, TUBA1A, RELN*, and other tubulin-related genes.[e4,e8] However, since those genes are not localized to the X chromosome, they are not further discussed here.

SBH Treatment

There are no specific ASMs recommended for SBH. Nonetheless, individual treatment strategies should be based on the type and frequency of seizures, EEG results, and ASM responsiveness. Surgical resection of heterotopic brain tissue

has been tried in a few individuals. Overall, it has not been effective in reducing seizures and thus is not recommended.[e9]

Periventricular Nodular Heterotopia

Periventricular nodular heterotopia (PNH) is a malformation of cortical development and is characterized by ectopic neuronal nodules, positioned along the lateral ventricles.[29] Drug-resistant seizures are a common finding appearing in adolescence and adulthood, manifesting in 50%–90% of patients.[30] Most patients have normal intelligence, but cognitive and developmental delay can also be observed. Reading impairments and dyslexia have been reported in patients with wider anatomic distribution of heterotopic nodules.[31]

PNH can be classified into classical and plus subtypes with classical PNH consisting of nodules located only along lateral ventricles while PNH plus includes periventricular nodules associated with other cortical and/or cerebral malformations.[29] In the classical form of PNH, epilepsy begins in the second decade of life with focal seizures that have a low frequency at onset. By contrast, in PNH-plus drug-resistant focal epilepsy can occur, alongside intellectual disability, and other neurologic deficits.

PNH Genetics

Many genetic variants have been associated with PNH, including deletions in chromosome 5 and monogenic variants like *ARFGEF2*.[32] PNH has also been associated with 22q11 deletion syndrome with presence of nodules located over the anterior horn of the lateral ventricles.[32] However, the classical form of PNH is mostly associated with the X-linked *FLNA* gene. Filamin A, the protein product of *FLNA*, is part of signaling pathways that mediate organogenesis during the embryonic phase. Patients with *FLNA* and PNH may also have several connective tissue abnormalities, including aortic aneurysm, patent ductus arteriosus, bicuspid aortic valve, cutaneous and joints abnormalities, and other features of Ehler-Danlos syndrome.[e10] About 50% of female individuals inherit the pathogenic genetic variant from their mother, and 50% will have a de novo pathogenic genetic variant.[e11] Owing to the X-linked inheritance pattern of *FLNA*, lethality during prenatal or neonatal periods often occurs in male individuals. However, variants in nonconserved regions of *FLNA* leading to milder phenotypes have been transmitted from mothers to sons and from fathers to daughters.[e12] More severe phenotypes in male individuals have also been reported.

PNH Treatment

No specific ASM has been shown to be better for PNH, compared with other forms of focal onset seizures. Patients presenting with refractory epilepsy may be eligible for resective or ablative surgery. This is especially true in patients where a single nodule is identified as the main epileptic generator and is located in a noneloquent area.[33] Scalp EEG-guided radio frequency thermocoagulation has also been used to achieve seizure reduction in 70% and seizure freedom in 16% of patients.[33]

PCDH19-Related Epilepsy

Previously known as epilepsy and mental retardation restricted to female individuals (EFMR) or "girls clustering epilepsy" (GCE), *PCDH19* variants cause an X-linked disorder almost exclusively affecting heterozygous female individuals.[34] The hallmark of *PCDH19*-related epilepsy is clusters of focal seizures, often triggered by fever, which may lead to a misdiagnosis of Dravet syndrome in the first few years of life.[35] These patients may also experience prolonged seizures with frequent status epilepticus.[35] However, as girls with *PCDH19*-related epilepsy grow older, their phenotype may become distinct from Dravet syndrome in that seizure cessation may occur as early as 2 years of age and as late as 35 years of age, with many adult patients reporting seizure freedom around school age to their early 20s.[36] By contrast, seizures in patients with Dravet syndrome usually persist, although with decreased frequency, and often more restricted to periods of sleep.[37]

Psychosis and schizophrenia are prominent features of adults with *PCDH19*-related conditions. In fact, pathogenic variants in *PCDH19* are the second most common cause of genetic schizophrenia.[35] Although psychotic episodes may take the form of auditory hallucinations and delusions, occurring as postictal phenomena, schizophrenia, and other forms of psychotic disorders can happen in patients who were seizure-free for many years when they develop their first psychiatric symptoms.[35] As such, individuals may require antipsychotic medications to control their symptoms.[35]

PCDH19 Genetics

PCDH19 is expressed in the hippocampi and cortex, but not in white matter. The resulting protein is thought to influence cell-cell adhesion. Most cases of *PCDH19*-related epilepsies are due to missense or nonsense variants that arise de novo in female individuals or are transmitted by nonaffected fathers.[36,38] Affected female patients are heterozygous for a deleterious variant, leading to cellular mosaicism. As such, one of the copies of this gene is inactive (due to CXI), in some but not all cells. The combination of cells with and without normal *PCDH19* product leads to "scrambling of cell-cell communication processes."[e13]

By contrast, male individuals are hemizygous, and as such they have a homogenous population of abnormal *PCDH19*. It is thought that in those male individuals, a nonparalogous Y-chromosome protocadherin (*PCDH11Y*) may partially compensate for the lack of *PCDH19*. However, rare cases of affected mosaic male patients have been reported in the literature with comorbid neuropsychiatric features and one report describing a trend toward increased behavioral symptoms with increasing age.[34,38,e14,e15]

PCDH19 Treatment

Combinations of drugs such as clobazam, valproic acid, and stiripentol are often used for treatment.[39] Recently, levetiracetam has shown great efficacy in adults and should be considered early in the management of refractory seizures caused by *PCDH19* with caution due to its known psychiatric side effects.[40]

Clinical trials have shown that oral ganaxolone, a synthetic analog of allopregnanolone, may reduce seizure frequency, is relatively safe and is well-tolerated in female patients aged 4–15 years.[41] Other trials verifying its clinical utility are ongoing. Epilepsy surgery can be considered to provide seizure freedom in select cases of patients with single seizure semiology.[42]

Aicardi Syndrome

Aicardi syndrome (AS) is diagnosed based on clinical features with the classic triad of agenesis of the corpus callosum, chorioretinal lacunae, and infantile spasms.[43] Other imaging features of this syndrome include polymicrogyria or pachygyria, cerebral asymmetry, choroid plexus papillomas, ventriculomegaly, and intracerebral cysts.[43]

Rapidly progressive scoliosis has been identified as a feature in children with AS, where bracing is ineffective.[44] In addition, patients typically have profound psychomotor delays and poor functional outcomes. Moderate-to-severe speech and language impairment are observed in almost all the reported cases of Aicardi syndrome.[45]

Epilepsy in AS can vary in severity and with seizure types, including infantile spasms, myoclonic, tonic, atonic, generalized tonic-clonic, atypical absence, focal seizures, and reflex audiogenic seizures.[45] Seizures usually appear between 3 and 4 months of age and are often asymmetric or unilateral.[43]

Genetics

AS is considered an X-linked disorder that predominantly affects female individuals. It has an estimated incidence of 1 in 100,000 live births.[43] Of interest, no X-linked causal gene has yet been found to explain the sex differences. Exome and genome sequencing of 10 female patients identified pathogenic de novo variants involving the genes *KMT2B, SLF1, SMARCB1, SZT2,* and *WNT8B*.[46] Some cases are associated with chromosomal translocations with breakpoints in the Xp22 region. Rare cases of male patients with "typical" AS-like phenotypes were found in male individuals with Klinefelter syndrome (XXY) and some typical XY male individuals.[43]

Treatment

While most seizures are drug resistant, one study found a 50% decrease from the median baseline number of seizures with cannabidiol.[47] In addition, completion of corpus callosotomy may also be considered as a palliative treatment for patients with partial agenesis of the corpus callosum.[48]

Recently, the effectiveness of the ketogenic diet as a means for seizure reduction in patients with drug-resistant epilepsies was evaluated.[49] It demonstrated short-term success where 93% of patients saw at least 50% seizure reduction after 3 months, which is greater than the usual response for ketogenic diet in other conditions.[49]

Recent clinical trials evaluated the role of reverse transcriptase inhibitors in AS, including drugs such as tenofovir, emtricitabine, abacavir, lamivudine, and zidovudine. Other active studies have looked at baricitinib as a therapeutic agent in patients with AS and other autoinflammatory conditions.[50,51]

Idiopathic Generalized Epilepsies

Idiopathic generalized epilepsies (IGE) are a group of epilepsies occurring in patients without a gross structural abnormality, onset occurring mainly in childhood and adolescence, normal intelligence and with an incidence of 2.9/100,000 per year.[52] Four well stablished syndromes make up the bulk of IGEs: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic-clonic seizures alone. Patients with these conditions have 1 or a combination of the following types of seizures: absence (with or without myoclonia), tonic-clonic, myoclonic-tonic-clonic, and myoclonic.[53] The incidence overall is slightly higher in female patients and is more frequently transmitted to offspring by affected mothers than by affected fathers.[53] The reason for this sex difference in IGEs is not well understood but is likely related to the complex interaction between genes, environment, and female hormones.[e16] JME is the most prevalent GGE in female patients with a higher female-to-male ratio.

Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy (JME) affects 5–10% of all patients with epilepsy, making it one of the most common epilepsy subtypes, and it affects female individuals more than male individuals.[54] Patients with JME present with myoclonic jerks, usually in the morning period, and tonic-clonic or myoclonic-tonic-clonic seizures.[54] Absence seizures may also occur and can be underestimated by patients.[54] It is estimated that 25%–42% of these patients have photosensitivity, and their seizures are often triggered by sleep deprivation, alcohol intake, menses, and cognitive tasks (praxis induction).[1,e17] Some patients with atypical JME, especially those belonging to multiplex families, may have very rarely astatic (atonic) seizures in addition to myoclonus, absence, and tonic-clonic.[e18] In addition to JME being more prevalent in female patients, female patients also have more absence seizures, triggered seizures, and photosensitivity. Furthermore, in female patients only, the presence of absence seizures, catamenial seizures, and stress-induced seizures were associated with drug-resistance, while photosensitivity was associated with seizure freedom.[1]

Genetics

JME is one of the most heritable forms of epilepsy; however, the precise mechanism of transmission is not clear. JME is

highly genetically determined, with concordance rates in monozygotic twins of up to 94%.[55] Furthermore, some familial forms of JME have a maternal transmission.[e16] In extremely rare families (less than 1%), JME is inherited in a Mendelian fashion.[55] Various JME-associated genes have been identified, including *EFHC1*, *CACNB4, CASR, GABRD, CLCN2*, and *GABRA1*.[55] Other studies have demonstrated polymorphisms in *GRM4, CX36*, and *BRD2* to be significantly associated with JME.[55] Further genetic abnormalities such as copy number variants have been described as a risk factor for JME.[55]

Recently, it was demonstrated that sporadic cases of genetic generalized epilepsies have a 4.5 higher burden of variants (as calculated by polygenic risk score) compared with controls.[56] A JME-specific increased polygenic risk score has not yet been demonstrated.

Treatment

Although JME is one of the most common types of epilepsies, to our knowledge, there are no double-blind randomized, placebo-controlled trials comparing different drugs looking specifically at JME. Some experts advocate for valproate as the most effective drug in treating JME, although this drug is generally avoided in female patients of childbearing age due to risk of fetal malformations.[54] There is conflicting evidence on the risk of seizure control in female patients of childbearing age using alternative ASMs to valproate. In a retrospective study that included 166 female patients with IGE, valproate alternatives were just as effective as valproate when used as monotherapy.[57] However, another study found that switching from valproate to an alternative ASM during pregnancy was associated with clinical worsening and unsatisfactory seizure control.[58]

Second-line therapies for the treatment of IGE include lamotrigine and levetiracetam. Although most epilepsy cases are easily managed with medication, some cases are refractory and there is a high risk of recurrence if attempting to wean off medication.[54] There have been clinical trials showing promising outcomes for seizure control in IGE with lacosamide[59] and perampanel.[60]

Genetic Counseling and Risk of Transmission

The knowledge of these genetic etiologies is important for genetic counseling, especially for affected individuals and their unaffected family members who plan to have children. In some cases, if the risk of transmission is high, preimplantation diagnosis can be offered. Moreover, most of these syndromes present in early childhood, and the long-term outcome is poorly known.

Conclusion

Genetic epilepsies in female individuals encompass a heterogenous group of disorders that, in most cases, are X-linked disorders. Genetics of the more common epilepsy syndrome of JME have a complex architecture, with rare families carrying a single-gene variant responsible for the phenotype. Most cases of familial and sporadic JMEs have a high polygenic risk burden for epilepsy. Hormones and environmental factors may also influence the expression of these epilepsies. To date, there is no specific treatment for most of these genetically determined epilepsies in female patients, although new medications and genetic disease-modifying therapies are being investigated. Understanding these sex-related differences is essential to recognize and individualize treatment in these patients. Advances in molecular genetics and diagnosis will lead to a better understanding of pathology, natural history of the disease, and hopefully tailored treatment of seizures and comorbidities in these conditions.

Author Contributions

P.T. Marques: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. N. Kaka: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. Q. Zulfiqar Ali: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Rong: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E. Bui: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. D.M. Andrade: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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References

1. Shakeshaft A, Panjwani N, Collingwood A, et al. Sex-specific disease modifiers in juvenile myoclonic epilepsy. *Sci Rep*. 2022;12(1):2785. doi:10.1038/s41598-022-06324-2
2. Deng X, Berletch JB, Nguyen DK, Disteche CM. X chromosome regulation: diverse patterns in development, tissues and disease. *Nat Rev Genet*. 2014;15(6):367-378. doi:10.1038/nrg3687
3. Shvetsova E, Sofronova A, Monajemi R, et al. Skewed X-inactivation is common in the general female population. *Eur J Hum Genet*. 2019;27(3):455-465. doi:10.1038/s41431-018-0291-3
4. Operto FF, Mazza R, Pastorino GMG, Verrotti A, Coppola G. Epilepsy and genetic in Rett syndrome: a review. *Brain Behav*. 2019;9(5):e01250. doi:10.1002/brb3.1250

5. Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan. *BMJ Paediatr Open*. 2020;4(1):e000717. doi:10.1136/bmjpo-2020-000717
6. Kadam SD, Sullivan BJ, Goyal A, Blue ME, Smith-Hicks C. Rett syndrome and CDKL5 deficiency disorder: from bench to clinic. *Int J Mol Sci*. 2019;20(20):5098. doi:10.3390/ijms20205098
7. Vashi N, Justice MJ. Treating Rett syndrome: from mouse models to human therapies. *Mamm Genome*. 2019;30(5-6):90-110. doi:10.1007/s00335-019-09793-5
8. Kyriakopoulos P, McNiven V, Carter MT, Humphreys P, Dyment D, Fantaneanu TA. Atypical Rett syndrome and intractable epilepsy with novel GRIN2B mutation. *Child Neurol Open*. 2018;5:2329048X18787946. doi:10.1177/2329048x18787946
9. Marafi D, Suter B, Schultz R, Glaze D, Pavlik VN, Goldman AM. Spectrum and time course of epilepsy and the associated cognitive decline in MECP2 duplication syndrome. *Neurology*. 2019;92(2):E108-E114. doi:10.1212/WNL.0000000000006742
10. Vignoli A, Savini MN, Nowbut MS, et al. Effectiveness and tolerability of antiepileptic drugs in 104 girls with Rett syndrome. *Epilepsy Behav*. 2017;66:27-33. doi:10.1016/j.yebeh.2016.10.006
11. Desnous B, Beretti T, Muller N, et al. Efficacy and tolerance of cannabidiol in the treatment of epilepsy in patients with Rett syndrome. *Epilepsia Open*. 2024;9(1):397-403. doi:10.1002/epi4.12796
12. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med*. 2023;29(6):1468-1475. doi:10.1038/s41591-023-02398-1
13. *NCT03633058. A Study to Evaluate Ketamine for the Treatment of Rett Syndrome*. clinicaltrials.gov/show/NCT03633058. cochranelibrary.com/central/doi/10.1002/central/CN-01662263/full
14. *A Novel, Regulated Gene Therapy (NGN-401) Study for Female Children with Rett Syndrome*. classic.clinicaltrials.gov/show/NCT05898620
15. Olson HE, Demarest ST, Pestana-Knight EM, et al. Cyclin-dependent kinase-like 5 deficiency disorder: clinical review. *Pediatr Neurol*. 2019;97:18-25. doi:10.1016/j.pediatrneurol.2019.02.015
16. Jakimiec M, Paprocka J, Śmigiel R. CDKL5 deficiency disorder—a complex epileptic encephalopathy. *Brain Sci*. 2020;10(2):107. doi:10.3390/brainsci10020107
17. Siri B, Varesio C, Freri E, et al. CDKL5 deficiency disorder in males: five new variants and review of the literature. *Eur J Paediatr Neurol*. 2021;33:9-20. doi:10.1016/j.ejpn.2021.04.007
18. Olson HE, Daniels CI, Haviland I, et al. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. *J Neurodev Disord*. 2021;13(1):40. doi:10.1186/s11689-021-09384-z
19. Müller A, Helbig I, Jansen C, et al. Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with CDKL5-related epilepsy. *Eur J Paediatr Neurol*. 2016;20(1):147-151. doi:10.1016/j.ejpn.2015.09.001
20. Aledo-Serrano Á, Gómez-Iglesias P, Toledano R, et al. Sodium channel blockers for the treatment of epilepsy in CDKL5 deficiency disorder: findings from a multicenter cohort. *Epilepsy Behav*. 2021;118:107946. doi:10.1016/j.yebeh.2021.107946
21. Devinsky O, King LT, Schwartz D, Conway E, Price D. Effect of fenfluramine on convulsive seizures in CDKL5 deficiency disorder. *Epilepsia*. 2021;62(7):e98-e102. doi:10.1111/epi.16923
22. Sullivan J, Gunning B, Zafar M, et al. Phase 2, placebo-controlled clinical study of oral ganaxolone in PCDH19-clustering epilepsy. *Epilepsy Res*. 2023;191:107112. doi:10.1016/j.eplepsyres.2023.107112
23. Demarest S, Jeste S, Agarwal N, et al. Efficacy, safety, and tolerability of soticlestat as adjunctive therapy for the treatment of seizures in patients with Dup15q syndrome or CDKL5 deficiency disorder in an open-label signal-finding phase II study (ARCADE). *Epilepsy Behav*. 2023;142:109173. doi:10.1016/j.yebeh.2023.109173
24. Terzic B, Davatolhagh MF, Ho Y, et al. Temporal manipulation of Cdkl5 reveals essential postdevelopmental functions and reversible CDKL5 deficiency disorder-related deficits. *J Clin Invest*. 2021;131(20):e143655. doi:10.1172/JCI143655
25. Hao S, Wang Q, Tang B, Wu Z, Yang T, Tang J. CDKL5 deficiency augments inhibitory input into the dentate gyrus that can be reversed by deep brain stimulation. *J Neurosci*. 2021;41(43):9031-9046. doi:10.1523/JNEUROSCI.1010-21.2021
26. Parrini E, Conti V, Dobyns WB, Guerrini R. Genetic basis of brain malformations. *Mol Syndromol*. 2016;7(4):220-233. doi:10.1159/000448639
27. Tan AP, Chong WK, Mankad K. Comprehensive genotype-phenotype correlation in lissencephaly. *Quant Imaging Med Surg*. 2018;8(7):673-693. doi:10.21037/qims.2018.08.08
28. Procopio R, Fortunato F, Gagliardi M, et al. Phenotypic variability in novel double-cortin gene variants associated with subcortical band heterotopia. *Int J Mol Sci*. 2024;25(10):5505. doi:10.3390/ijms25105505
29. Paliotti K, Dassi C, Berrahmoune S, et al. The phenotypic spectrum of epilepsy associated with periventricular nodular heterotopia. *J Neurol*. 2023;270(8):3934-3945. doi:10.1007/s00415-023-11724-z
30. Liu W, Yan B, An D, Xiao J, Hu F, Zhou D. Sporadic periventricular nodular heterotopia: Classification, phenotype and correlation with Filamin A mutations. *Epilepsy Res*. 2017;133:33-40. doi:10.1016/j.eplepsyres.2017.03.005
31. Passarelli V, Moreira CH. Periventricular nodular heterotopia: pathogenesis, epileptogenesis and implications in higher cerebral functions. *Mol Cell Epilepsy*. 2014. doi:10.14800/mce.20
32. Rezazadeh A, Bercovici E, Kiehl TR, et al. Periventricular nodular heterotopia in 22q11.2 deletion and frontal lobe migration. *Ann Clin Transl Neurol*. 2018;5(11):1314-1322. doi:10.1002/acn3.641
33. Khoo HM, Gotman J, Hall JA, Dubeau F. Treatment of epilepsy associated with periventricular nodular heterotopia. *Curr Neurol Neurosci Rep*. 2020;20(12):59. doi:10.1007/s11910-020-01082-y
34. Samanta D. PCDH19-related epilepsy syndrome: a comprehensive clinical review. *Pediatr Neurol*. 2020;105:3-9. doi:10.1016/j.pediatrneurol.2019.10.009
35. Vlaskamp DRM, Bassett AS, Sullivan JE, et al. Schizophrenia is a later-onset feature of PCDH19 girls clustering epilepsy. *Epilepsia*. 2019;60(3):429-440. doi:10.1111/epi.14678
36. Cappelletti S, Specchio N, Moavero R, et al. Cognitive development in females with PCDH19 gene-related epilepsy. *Epilepsy Behav*. 2015;42:36-40. doi:10.1016/j.yebeh.2014.10.019
37. Selvarajah A, Zulfiqar-Ali Q, Marques P, Rong M, Andrade DM. A systematic review of adults with Dravet syndrome. *Seizure*. 2021;87:39-45. doi:10.1016/j.seizure.2021.02.025
38. Johannessen M, Kjellsen IM, Malt E. Behavioral and neuropsychological profile of a male patient with mosaic PCDH19 mutation. *Epilepsy Behav Rep*. 2022;19:100559. doi:10.1016/j.ebr.2022.100559
39. Lotte J, Bast T, Borusiak P, et al. Effectiveness of antiepileptic therapy in patients with PCDH19 mutations. *Seizure*. 2016;35:106-110. doi:10.1016/j.seizure.2016.01.006
40. Sadleir LG, Kolc KL, King C, et al. Levetiracetam efficacy in PCDH19 girls clustering epilepsy. *Eur J paediatric Neurol*. 2020;24:142-147. doi:10.1016/j.ejpn.2019.12.020
41. Lappalainen J, Chez M, Sullivan J, Gecz J, Specchio N, Patroneva A. A multicenter, open-label trial of ganaxolone in children with PCDH19 epilepsy (P5.236). *Neurology*. 2017;88(16_supplement):P5-P236. doi:10.1212/wnl.88.16_supplement.p5.236
42. Simmons R, Singhal N, Sullivan J, et al. Epilepsy surgery as a treatment option for select patients with PCDH19-related epilepsy. *Epilepsy Behav*. 2023;149:109517. doi:10.1016/j.yebeh.2023.109517
43. Wong BKY, Sutton VR. Aicardi syndrome, an unsolved mystery: review of diagnostic features, previous attempts, and future opportunities for genetic examination. *Am J Med Genet C Semin Med Genet*. 2018;178(4):423-431. doi:10.1002/ajmg.c.31658
44. Grigoriou E, DeSabato JJ, Colo D, Dormans JP. Scoliosis in children with Aicardi syndrome. *J Pediatr Orthop*. 2015;35(5):e38-e42. doi:10.1097/BPO.0000000000000368
45. Tuft M, Østby Y, Nakken KO, Lund C. Aicardi syndrome and cognitive abilities: a report of five cases. *Epilepsy Behav*. 2017;73:161-165. doi:10.1016/j.yebeh.2017.05.002
46. Ha TT, Burgess R, Newman M, et al. Aicardi syndrome is a genetically heterogeneous disorder. *Genes (Basel)*. 2023;14(8):1565. doi:10.3390/genes14081565
47. Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav*. 2018;86:131-137. doi:10.1016/j.yebeh.2018.05.013
48. Bernstock JD, Olsen HE, Segar D, et al. Corpus callosotomy for refractory epilepsy in Aicardi syndrome: case report and Focused review of the literature. *World Neurosurg*. 2020;142:450-455. doi:10.1016/j.wneu.2020.06.230
49. Sanchez MAR, Cervenka MC, Bessone SK, Kossoff EH. Ketogenic diet therapy for epilepsy associated with Aicardi syndrome. *J Child Neurol*. 2021;36(11):1007-1010. doi:10.1177/08830738211023335
50. *JAK Inhibitor Treatment in AGS*. clinicaltrials.gov/study/NCT03921554?tab=history&a=1
51. Vanderver A, Adang L, Gavazzi F, et al. Janus kinase inhibition in the Aicardi-Goutières syndrome. *N Engl J Med*. 2020;383(10):986-989. doi:10.1056/NEJMc2001362
52. Gesche J, Christensen J, Hjalgrim H, Rubboli G, Beier CP. Epidemiology and outcome of idiopathic generalized epilepsy in adults. *Eur J Neurol*. 2020;27(4):676-684. doi:10.1111/ene.14142
53. Asadi-Pooya AA, Homayoun M. Sex differences in characteristics of idiopathic generalized epilepsies. *Neurol Sci*. 2021;42(6):2421-2424. doi:10.1007/s10072-020-04834-3
54. Brodie MJ. Modern management of juvenile myoclonic epilepsy. *Expert Rev Neurother*. 2016;16(6):681-688. doi:10.1080/14737175.2016.1179113
55. Santos BPD, Marinho CRM, Marques TEBS, et al. Genetic susceptibility in juvenile myoclonic epilepsy: systematic review of genetic association studies. *PLoS One*. 2017;12(6):e0179629. doi:10.1371/journal.pone.0179629
56. Leu C, Stevelink R, Smith AW, et al. Polygenic burden in focal and generalized epilepsies. *Brain*. 2019;142(11):3473-3481. doi:10.1093/brain/awz292
57. Kiiski R, Basnyat P, Raitanen J, Rainesalo S, Peltola J, Mäkinen J. Treatment outcomes in women with idiopathic generalized epilepsy. *Acta Neurol Scand*. 2022;145(4):423-433. doi:10.1111/ane.13567
58. Cerulli Irelli E, Morano A, Cocchi E, et al. Doing without valproate in women of childbearing potential with idiopathic generalized epilepsy: Implications on seizure outcome. *Epilepsia*. 2020;61(1):107-114. doi:10.1111/epi.16407
59. Vossler DG, Knake S, O'Brien TJ, et al. Efficacy and safety of adjunctive lacosamide in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. *J Neurol Neurosurg Psychiatry*. 2020;91(10):1067-1075. doi:10.1136/jnnp-2020-323524
60. Villanueva V, Montoya J, Castillo A, et al. Perampanel in routine clinical use in idiopathic generalized epilepsy: the 12-month GENERAL study. *Epilepsia*. 2018;59(9):1740-1752. doi:10.1111/epi.14522

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