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REVIEW

Epilepsy in Angelman syndrome

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Summary Angelman syndrome is a neurogenetic disorder caused by lack of *UBE3A* gene expression from the maternally inherited chromosome 15 due to various 15q11-q13 abnormalities. In addition to severe developmental delay, virtual absence of speech, motor impairment, a behavioural phenotype that includes happy demeanour, and distinctive rhythmic electroencephalographic features, over 90% of patients have epilepsy. Many different seizure types may occur, atypical absences and myoclonic seizures being particularly prevalent. Non-convulsive status epilepticus is common, sometimes in the context of the epileptic syndrome referred to as myoclonic status in non-progressive encephalopathies. Epilepsy predominates in childhood, but may persist or reappear in adulthood. Management is difficult in a proportion of patients. It might be improved by better understanding of pathophysiology. Current hypotheses involve abnormal inhibitory transmission due to impaired regulation of GABAA receptors related to functional absence of UBE3A and abnormal hippocampal CaMKII activity.
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Interest in monogenic disorders with epilepsy has provided significant insights into the pathophysiology of epilepsy. Among these disorders, Angelman syndrome has attracted particular attention because of its complex genetics. Angelman syndrome is characterised by developmental delay, absence of speech, motor impairment, epilepsy and a peculiar behavioural phenotype with apparent happy demeanour. It is caused by the lack of expression of the *UBE3A* gene, which can result from various abnormalities of chromosome 15q11-q13. Similar abnormalities of chromosome 15q11-q13 result either in Angelman syndrome if they concern the chromosome inherited from the mother, or in Prader-Willi syndrome (a clinically distinct condition with hypotonia, learning difficulties, obesity and hypogonadism), if they concern the chromosome of paternal origin. The factor determining the phenotypic outcome is the parental origin of the chromosome 15 defect, illustrating the phenomenon of genomic imprinting. In about 70% of patients, Angelman syndrome is due to a *de novo* 15q11-q13 deletion on the chromosome inherited from the mother.[1] This deletion cannot be identified with routine chromosome studies but it can be detected with fluorescence in situ hybridisation (FISH) using appropriate probes. Approximately 2—3% of patients have inherited both copies of chromosome 15 from the father and none from the mother, i.e. paternal uniparental disomy.[2] As a result, no functional copy of the *UBE3A* gene is inherited from the mother. In contrast to patients with a deletion, those with uniparental disomy have a statistically less severe phenotype.[3] They have a low incidence of microcephaly, less severe seizures and have more words, although speech is extremely limited and not used as a main communication tool. Another 3—5% of patients have an imprinting defect resulting in a lack of the typical maternal pattern of DNA methylation.[4] Statistically, the phenotype of patients with an imprinting defect is indistinguishable form that of patients with uniparental disomy.[3] There is a mutation in the maternal *UBE3A* gene[5,6] in another 5—10% of patients. Most of them appear to be private mutations, with a high occurrence rate of *de novo* mutations. Finally, in up to 10% of typical cases, no cytogenetic or molecular abnormality can currently be found.

Overall, seizures occur in about 90% of patients with Angelman syndrome. They are the most frequent cause of hospital admission.[7] Unprovoked and provoked seizures may coexist. As mentioned above, epilepsy is often more severe in patients who have a chromosome 15q11-q13 deletion (including genes coding for $GABA_A$ receptor subunits) than in those in other molecular classes.[8,9] This is consistent with generally milder neurobehavioural features in patients without a deletion.[3] Nevertheless, seizures tend to have a similar pattern whatever the molecular class, with occurrence in clusters alternating with seizure-free periods. The clusters occur apparently spontaneously or they may be precipitated by factors such as infection, excitement, physical effort, intense fatigue, etc.

Natural history of the seizure disorder

Onset of seizures is often before 3 years of age, mostly between 1 and 3 years.[10—13] Whereas epilepsy is often a prominent clinical problem in childhood, seizure onset occurs during infancy in a minority of patients. Less than 25% develop seizures before 12 months of age[11]; 30% before 24 months.[12] If seizures do occur in infants, they tend to do so in a febrile context. In a high proportion of patients, the onset of epilepsy precedes the diagnosis of Angelman syndrome.[14] Seizure types may evolve with age.[15,16] As in other developmental conditions with epilepsy, the seizure disorder often improves in late childhood. Sustained seizure-freedom following epilepsy in childhood has been found in four of five patients with a 15q11-q13 deletion followed up longitudinally until the age of 30 years or more.[16] Other studies, however, have shown that epilepsy can persist or reappear in adulthood.[7,17] For example, seizures were found to be the most prevalent clinical problem in a group of adolescents and adults, occurring in 11 of 28 surveyed patients (aged 16—40 years).[18] Following a relatively quiescent phase in the teenage years, eight of these patients had an increase in seizures, which became difficult to control during their mid-twenties. Laan et al.[19] found that 23 of 28 the adults they studied (aged 20—53 years) had seizures.

Seizure types

Many different types of seizures have been reported, both generalised and focal. They include epileptic spasms, myoclonic absences, myoclonic, atonic, tonic and tonic—clonic seizures.[8,15,20—24] Atypical absence and myoclonic seizures have been particularly emphasised. In contrast, epileptic spasms are uncommon. Multiple seizure types occur in about half of the patients with a 15q11-q13 deletion.[14]

Patterns of seizures, including type, age of onset, other clinical features and electroencephalographic features of patients with Angelman syndrome may show some resemblance with defined epileptic syn-

dromes. In this context, it is important to characterise their epilepsy correctly given implications for both management and prognosis. Although epileptic spasms are the typical seizure type of West syndrome or infantile spasms (in association with hypsarrhythmic electrencephalogram and 'developmental arrest'), this epileptic syndrome has rarely been documented convincingly in Angelman syndrome. In the vast majority of cases, the electrencephalographic patterns seen in Angelman syndrome can be differentiated easily from hypsarrhythmia.[25] The most commonly identified of these typical patterns consists of runs of rhythmic 2–3/s activity of high amplitude often exceeding 300 μV seen mainly over the frontal regions,[21,26–29] i.e. Pattern I in Dan and Boyd's classification.[25] Studying this electroencephalographic pattern, Valente et al.[28] noted that it may rarely present in the form of a 'hypsarrhythmic-like' variant consisting of runs of high amplitude asynchronous delta activity associated with multifocal spikes or sharp waves of moderate amplitude. These authors emphasised the differences between this feature and hypsarrhythmia, e.g. fragmentation of hypsarrhythmia during sleep. Nevertheless, although Bower and Jeavons had differentiated their electroencephalographic findings in early reported patients with Angelman syndrome from hypsarrhythmia,[30] some authors have inappropriately referred to the rhythmic electroencephalographic patterns seen in Angelman syndrome, particularly Pattern I, as 'hypsarrhythmia'. This is misleading, as it may result in wrong diagnosis and inadequate treatment.

Similarly, although tonic seizures and complex absences can occur in Angelman syndrome, confusion with Lennox-Gastaut syndrome can be avoided without much difficulty in many cases. Confusion with the electroencephalographic features of Lennox-Gastaut syndrome has also arisen in some reports, although the runs of slow spike–wave complexes seen in Angelman syndrome are usually rhythmic and signal non-convulsive status epilepticus (which has no specific features and is indeed indistinguishable from that seen in Lennox-Gastaut). Nevertheless, this label has been misused in a number of reports.

In contrast, another epileptic syndrome, referred to as myoclonic status in non-progressive encephalopathies, has been appropriately recognised in a number of patients with Angelman syndrome.[31] This syndrome is characterised by recurrent episodes of myoclonic status in patients who have pre-existing non-progressive neurological deficits including severe intellectual disability, axial hypotonia and ataxia.[32] It also occurs in Wolff-Hirschhorn syndrome (4p-syndrome), neonatal encephalopathy and metabolic disorders such as non-ketotic hyperglycinaemia.

Another condition, which is not an epileptic syndrome *stricto sensu* in the absence of seizures, is electric status epilepticus during sleep, also known as continuous spike–wave discharges during sleep. The electroencephalographic features consists of generalised slow (usually around 2/s) spike–wave complexes, sometimes with a frontal emphasis, occupying more than 85% of slow-wave sleep, while this activity is exceedingly rare in rapid eye movement sleep. When the triad of electroencephalographic continuous spike–wave discharges during sleep, seizures (all types can occur except for tonic seizures) and impairment of neuropsychological and motor (e.g. ataxia) function is present, the condition can be regarded as an epileptic syndrome termed 'epilepsy with continuous spike–wave discharges during sleep'. This syndrome has rarely been documented in Angelman syndrome.[33] The lack of clinical alteration concomitant to the electrographic epileptiform activity excludes it from the context of non-convulsive status epilepticus.[34]

Both convulsive and non-convulsive status epilepticus may occur. Compared to other conditions with epilepsy, the latter is relatively common, including in cases that are not due to 15q11-q13 deletion.[15,16,20,21,27,35] Although non-convulsive status epilepticus appears to be more common during childhood, it can occur in infancy[36] and adulthood.[37] Electroencephalogram shows continuous epileptic discharges which are distinct from the typical rhythmic electroencephalographic features of Angelman syndrome.[25] The distinction between generalised and complex partial non-convulsive status epilepticus is often difficult to make. The term 'dialeptic status epilepticus', which refers to seizure phenomenology with alteration of consciousness as main ictal feature without any reference to the origin, might appear more appropriate in this context.[34] Frequent or prolonged episodes of dialeptic status epilepticus may contribute to a poor cognitive outcome, as suggested in other conditions with epilepsy.[38]

In some cases, prolonged disabling tremor has been ascribed to cortical myoclonus[39] or myoclonic status.[36] Such disabling resting tremor may appear in day-long clusters, particularly in adolescents or adults.[18,40] When severe, it may result in loss of ability to eat or walk independently during episodes. The aetiology of this tremor remains unclear. It seems to be non-epileptic in a number of cases. In one report of two adult patients, associated cogwheel-type rigidity and bradykinesia suggested Parkinsonism and tremor improved dramatically on levodopa.[41] In another young adult, episodes of

generalised shaking predominating in the upper extremities were correlated with 4—10/s electromyographic bursts but no ictal electroencephalographic changes.[42] The electromyographic features were similar to the postural bursting activity described in children with Angelman syndrome,[43] although the latter was not associated with actual tremor. The muscle activity associated with the movements was so intense that it induced hyperthermia and rhabdomyolysis. The movements were effectively controlled by reserpine in association with topiramate. This prominent, quasi-clonic activity may be difficult to distinguish from myoclonus. In a few other cases, fast-bursting myoclonus has been correlated with electroencephalographic activity of similar frequency or at subharmonics, suggesting cortical myoclonus[36,39] similar to findings in Rett syndrome.[44,45] Guerrini et al.[39] reported response to piracetam. We did not find any response to either piracetam or levetiracetam in four of our patients.

Finally, it must be noted that absence of electroencephalographic discharges correlated with bouts of laughter suggests that they do not correspond to gelastic seizures. Similarly, Sugimoto et al.[35] found no electroencephalographic changes during head drops. Other possibly challenging spells include stereotyped movements, tremors, staring episodes, eye rolling, motor/behavioural manifestations of gastro-oesophageal reflux (Sandifer syndrome) and self-gratification episodes ('masturbation').

Pathophysiology

Although the seizure disorder has been one of the most studied aspects of Angelman syndrome, the underlying pathophysiology is still a matter of speculation. Like many other features of Angelman syndrome, it has been hypothesised to be related to dysfunction of the $GABA_A$ receptor complex, primarily because the commonly deleted region of chromosome 15q11-q13 contains a cluster of genes for three of its subunits (α5, β3 and γ3). Deficits in this receptor have been related to neurodevelopmental impairment and seizure disorder.[46—48] The $GABA_A$ receptor is associated with a gated chloride channel. In the mature brain, it plays a major role in inhibitory neurotransmission. It is constituted by a heteropentameric arrangement of individual subunits from seven families (α, β, γ, δ, ε, σ and π). The subunit composition of the heteropentameric complex shows marked developmental changes. It may affect the receptor properties, including kinetic characteristics and the effects of allosteric modulators (e.g. zinc, neurosteroids and benzodiazepines). Subunits α, β and γ exist in multiple isoforms. As a result, a great number of different isoforms of $GABA_A$ receptor are possible. The *GABRB3*, *GABRG3* and *GABRA5* genes, which code for three subunits of the $GABA_A$ receptor (α5, β3 and γ3, respectively) are clustered in the 15q11-q13 region. These genes are expressed in several regions of the adult brain and are even more abundant in many regions of the embryonic and neonatal brain.[49] All known $GABA_A$ receptor subtypes contain a β subunit and β3 is the only one present early in life.[49] Absence of a copy of the *GABRB3*, *GABRG3* and *GABRA5* genes has tentatively been related to abnormalities in GABAergic neurotransmission.[46] Knockout mice for *Gabrb3*, *Gabrg3* and *Gabra5*[50] or for *Gabrb3* alone[51] have been proposed as animal models for Angelman syndrome. The most relevant of these models appears to be that produced by disruption of the β3 subunit gene in mice, leading to epilepsy and other abnormalities that show similarities to Angelman syndrome.[51] However, *GABRB3* disruption does not account for all features of Angelman syndrome. For example, patients with 15q11-q13 cytogenetic alterations, such as deletions on the paternally derived chromosome (Prader-Willi syndrome), pericentromeric inversions and duplications (inv-dup(15) syndrome) or other types of duplications (in some cases of autism), have distinct clinical phenotypes. Furthermore, about 30% of patients with Angelman syndrome do not have a deletion involving the *GABRB3* gene, i.e. patients with imprinting defect, uniparental disomy, *UBE3A* mutation or no detectable 15q11-q13 abnormality. Although there is no evidence of imprinting of the *GABRB3* gene in humans, a recent study suggested that there might be some (subtle) influence of parent of origin and of gender in whole brain β3 subunit levels in *Gabrb3*-deficient heterozygous mice.[52]

In contrast, all patients with a molecular diagnosis of Angelman syndrome have a functional absence of the maternally inherited *UBE3A* gene. The gene product (UBE3A) acts as an E3 ubiquitin—protein ligase along the ubiquitin pathway.[53] The best-characterised function of ubiquitination is to mark target proteins for specific proteolysis by proteasomes. Ubiquitin-mediated proteolysis may be important in a number of neuronal processes, including synpatogenesis and mechanisms of long-term memory. Ubiquitination pathways have been implicated in the pathophysiology of other neurological disorders than Angelman syndrome.[54] For example, early-onset autosomal recessive Parkinson disease is due to abnormalities of the gene coding for parkin, another E3 ubiquitin—protein ligase.[55] In addition, the ubiquitin pathway may also be

involved in the regulation of the abundance of postsynaptic receptors.[56] It has been suggested that functional absence of UBE3A would impair the regulation of $GABA_A$ receptors.[25,57] In this hypothesis, altered regulation of β3 subunit-containing $GABA_A$ receptors would lead to 'compensation' involving isoforms of the $GABA_A$ receptor which do not contain the β3 subunit.[58] This might result in changes in the receptors' kinetics and desensitisation properties.[59] Although these changes are expected to be subtle, they may have extensive effects during brain maturation as well as through the patient's life.

Alternative or additional mechanisms of epileptogenesis possibly involve abnormal intracellular calcium signalling, including abnormal Ca^{++}/calmodulin-dependent protein kinase II.[60,61] Other, less specific mechanisms are likely to play major roles in epilepsy seen in Angelman syndrome and other neurodevelopmental disorders, particularly those with intellectual disability, whether or not due to chromosome abnormalities. However, very little is currently known about these mechanisms. Synaptic mechanisms are mostly understood as affecting some 'balance' between excitatory and inhibitory influences. As mentioned above, the focus in Angelman syndrome has been directed on $GABA_A$-mediated inhibition. Synaptic modulation and plasticity probably deserve more attention. In addition, the potential role of non-synaptic mechanisms of neuronal synchrony, such as gap junctions, has not been investigated (except in the cerebellum[62]).

Management

Seizures may be difficult to control with pharmacological treatment, particularly in childhood. However, in a study of 68 patients, 91% of whom had epilepsy, 43% were controlled by the initial therapeutic option.[63] Surveys of antiepileptic drugs used in patients with Angelman syndrome have suggested that sodium valproate is the most commonly used.[64] The use of clonazepam has also been reported in a number of cases. These drugs have been recommended on the basis of early reports of retrospective, open studies of limited patient series. The effectiveness of other benzodiazepines, such as nitrazepam and clobazam, seems to be similar to that of clonazepam in patients with Angelman syndrome.[9] However, in the majority of patients, the use of benzodiazepines does not appear to be justified as a first-line treatment. Phenobarbitone can be both effective and well tolerated in infants. Because of sedative or cognitive side effects, it is less used in children and older patients. However, Clayton-Smith and Laan[65] have suggested that it may be a good option in adults. Levetiracetam, topiramate, ethosuximide and lamotrigine have been successfully used in many cases, but there is a lack of controlled studies. It is noteworthy that although lamotrigine drug has no direct effect on $GABA_A$ receptors,[66] it might promote *GABRB3* gene expression in hippocampal cells.[67]

Some antiepileptic drugs may be paradoxically detrimental through increase in the risk of seizures, facilitation of the development of other seizure types or precipitation of non-convulsive status epilepticus. These drugs include carbamazepine,[8,14,19] oxcarbazepine,[14] vigabatrin,[9,14,68] tiagabine and probably gabapentin. However, this observation does not imply absolute contraindication of these drugs, which may prove useful in some patients. This aggravation due to antiepileptic drugs is not specific to Angelman syndrome, where it appears to be more marginal than in some epileptic syndrome, notably idiopathic generalised epilepsies.

Response of non-convulsive status epilepticus to treatment is variable and management may be difficult. Oral benzodiazepines, corticosteroids and ketamine[69] may be early options, but there has been a marked lack of well-designed studies. Morbidity associated with aggressive treatment may outweigh the risk of therapeutic abstention. In contrast, convulsive status epilepticus requires early effective treatment according to common treatment protocols.

Non-pharmacological management is rarely considered, despite the relatively high prevalence of drug resistance. Ketogenic diet was effective in four patients with refractory epilepsy in Valente et al.'s[14] series.

Conclusion

Patients with Angelman syndrome have an increased risk of epilepsy. Compared to many other neurodevelopmental disorders, the risk seems remarkably high. In particular, early-childhood onset of refractory epilepsy with atypical absences and myoclonic seizures with predisposition to developing non-convulsive status epilepticus is a common presentation. This may be due to propensity to hypersynchronous neuronal activity, which might be related to abnormal GABA-mediated transmission due to lack of *UBE3A* expression, or other factors. In recent years, there has been increasing awareness of the possibility of seizure disorder in adult patients. However, epilepsy may be difficult to diagnose. On the one hand, non-epileptic stereotyped or paroxysmal events (including motor or behavioural manifestations) may lead to overdiagnosis. On the other hand,

the epileptic nature of relatively subtle manifestations such as absences, myoclonias or non-convulsive status epilepticus may be under-recognised in the context of behavioural and motor features. The neurocognitive effects of seizures are difficult to evaluate. There is a major need for evidence on which to base rational treatment.

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