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CRITICAL REVIEW AND INVITED COMMENTARY

Angelman syndrome: Current understanding and research prospects

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Summary

Angelman syndrome is a neurogenetic disorder characterized by developmental delay, severe intellectual disability, absent speech, exuberant behavior with happy demeanor, motor impairment, and epilepsy, due to deficient *UBE3A* gene expression that may be caused by various abnormalities of chromosome 15. Recent findings in animal models demonstrated altered dendritic spine formation as well as both synaptic [including γ-aminobutyric acid $(GABA)_A$ and *N*-methyl-D-aspartate (NMDA) transmission] and nonsynaptic (including gap junction) influences in various brain regions, including hippocampus and cerebellar cortex. Reversal of selected abnormalities in rescue genetically engineered animal models is encouraging, although it should not be misinterpreted as promising "cure" for affected patients. Much research is still required to fully understand the functional links between lack of *UBE3A* expression and clinical manifestations of Angelman syndrome. Studies of regulation of *UBE3A* expression, including imprinting-related methylation, may point to possibilities of therapeutic upregulation. Understanding relevant roles of the gene product might lead to targeted intervention. Further documentation of brain network dynamics, with particular emphasis on hippocampus, thalamocortical, and cerebellar networks is needed, including in a developmental perspective. There is also a need for further clinical research for improving management of problems such as epilepsy, behavior, communication, learning, motor impairment, and sleep disturbances.

KEY WORDS: Angelman syndrome, UBE3A, GABA, NMDA, Gap junction, Epilepsy.

Angelman syndrome was first recognized some 45 years ago in three unrelated children who presented with similar behavioral features and developmental profile, described as "puppet children" (Angelman, 1965). All three had microbrachycephaly, severe intellectual disability, frequent and easily provoked bouts of laughter, absence of speech, tongue protrusion, hypotonia, increased knee jerks, unsteadiness, ataxia, and epilepsy. Harry Angelman thus typified a clinical model for a condition that includes a behavioral phenotype before the concept was formalized and used to identify the genetic basis of conditions such as fragile X syndrome, Rett syndrome and, of course, Angelman syndrome itself. Over the 10 years following the original description, only 11 additional patients were recorded in the international literature. Interest for the syndrome increased dramatically from the mid-1980s, following stimulating findings in genetics and clinical neurophysiology. By 1990, more than 150 patients had been described and since then several hundreds more. This issue of *Epilepsia* features two surveys conducted in further large series of patients, one focusing on natural history and treatment of epilepsy (Thibert et al., 2009) and the other on sleep disturbances and their association with epilepsy (Conant et al., 2009). Occurrence is mostly sporadic, with estimated prevalence between 1:10,000 and 1:40,000 (Petersen et al., 1995; Thomson et al., 2006). A comprehensive monograph on the syndrome was recently published (Dan, 2008). Recent insights into molecular genetics and neurophysiology have raised hopes for breakthroughs in the management of patients with Angelman syndrome. The present review addresses clinical, neurophysiologic, and genetic aspects of the syndrome and presents perspectives for future research.

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Clinical Features

The clinical picture has been broadly documented, principally in children, but with an increasing emphasis on adolescents and adults. Clinical diagnosis is based on a set of physical (Fig. 1) and behavioral features (Williams et al., 2006) (Table 1). All patients have developmental delay with severely impaired cognitive skills, although accurate assessment is often difficult. They show specific speech impairment; about one-third of patients speak no words at all, and the others rarely use more than five words. This contrasts with better receptive verbal communication and communication skills based on spontaneous or learned signs (Clayton-Smith, 1993; Trillingsgaard & Østergaard, 2004). Behavior is characteristically overactive, exuberant, sociable, and happy, with frequent smiling and laughing (Pelc et al., 2008a). Developmental motor impairment includes mild to moderate axial hypotonia, present from birth, and eventual spastic hypertonia of the limbs that may become apparent during the first year of life (Dan & Cheron, 2008). Despite varying degrees of ataxia, most patients develop independent walking. Gait is distinctive, with a wide support base, extension and lateral rotation of the lower limb, elbow flexion, and wrist supination. About 90% of patients have epileptic seizures (Pelc et al., 2008b; Thibert et al., 2009). Seizure onset is often between 1 and 3 years. Many seizure types, both generalized and focal, have been reported, including epileptic spasms, myoclonic absences, myoclonic, atonic, tonic, and tonic–clonic seizures (Viani et al., 1995; Laan et al., 1997; Pelc et al., 2008b; Thibert et al., 2009), but atypical absence and myoclonic seizures have been particularly emphasized. As in other developmental conditions with epilepsy, the seizure disorder often improves in late childhood, although epilepsy can persist or reappear in adulthood, and be difficult to control. Both convulsive and nonconvulsive status epilepticus may occur. The latter is particularly common during childhood, but it can occur in infancy (Ogawa et al., 1996) and adulthood (Espay et al., 2005). In adolescents and adults, particularly, prolonged disabling tremor has been ascribed to cortical myoclonus (Guerrini et al., 1996) or myoclonic status (Ogawa et al., 1996; Elia, 2009). Eventual response to piracetam (Guerrini et al., 1996) cannot be taken in itself as supporting an epileptic basis, given the multiple effects of this drug, including in movement disorders. The underlying mechanism remains unclear. It seems to be nonepileptic at least in some cases, where response to levodopa (Harbord, 2001), reserpine, or topiramate (Stecker & Myers, 2003) has been documented. Sleep problems commonly reduced total sleep time, increased sleep onset latency, disrupted sleep architecture with frequent nocturnal awakenings, reduced rapid eye movement (REM) sleep, and periodic leg movements (Didden et al.,2004; Miano et al., 2005; Walz et al., 2005; Pelc et al., 2008c; Conant et al., 2009).

Figure 1.
Facial characteristics of a child with Angelman syndrome. Note visual contact, fair eyes, pointed nose, midface hypoplasia, wide smiling mouth, prognathism, and sialorrhea.

Neurophysiologic Features

The contribution of EEG to diagnosis of Angelman syndrome has been recognized in both children (Boyd et al., 1988; Rubin et al., 1997; Korff et al., 2005) and adults (Sandanam et al., 1997; Van Buggenhout et al., 2000), and particularly highlighted in infants (Van Lierde et al., 1990). In contrast to the paucity of physiologic rhythms, interictal EEG shows three distinctive high-amplitude rhythmic patterns (Dan & Boyd, 2003), which can reinforce the clinical diagnosis (Williams et al., 2006). The most commonly identified EEG abnormality (pattern I) consists of runs of high amplitude rhythmic 2–3 Hz (delta) activity, seen mainly over the frontal regions (Fig. 2A). A variant composed of sharp slow waves has been characterized as ''triphasic'' (Laan et al., 1997), ''triphasic-like'' (Valente et al., 2003), ''polyphasic slow waves'' (Minassian et al., 1998), ''pattern IB'' (Dan & Boyd, 2003), or ''notched delta'' (Korff et al., 2005). Another pattern consisting of prolonged runs of rhythmic 4–6 Hz (theta) activity with centrotemporal emphasis (pattern II, Fig. 2B) is common in young children (Rubin et al., 1997), but tends to disappear after 5 (Boyd et al., 1988) to 12 (Laan et al., 1997) years of age. Pattern III consists of high amplitude 3–6/s rhythmic activity sometimes containing small spikes, predominating over posterior regions (Fig. 2C). Eye closure facilitates its occurrence (Boyd et al., 1988; Viani et al., 1995; Rubin et al., 1997).

Table 1. Clinical diagnostic criteria for Angelman syndrome

A. Consistent features (100%)	B. Frequent features (more than 80%)	C. Associated features (20–80%)
Developmental delay, functionally severe	*Delayed growth in head circumference*, usually resulting in microcephaly by 2 years of age. Microcephaly is more pronounced in patients with 15q11-q13 microdeletion	Flat occiput
Movement or balance disorder, usually ataxia of gait, and/or tremor. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions	*Seizures*. Severity usually decreases with age but the seizure disorder lasts throughout life	Occipital groove
Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotor behavior	*Abnormal EEG*, with a characteristic pattern (Dan & Boyd, 2003). EEG abnormalities can occur in the first 2 years of life, can precede clinical features, and are often not correlated to clinical seizures	Protruding tongue
Speech impairment, none or minimal use of words; receptive and non-verbal communication skills better than verbal ones		Tongue thrusting; suck/swallowing disorders
		Feeding problems and/or truncal hypotonia during infancy
		Prognathism
		Wide mouth, wide-spaced teeth
		Frequent drooling
		Excessive chewing/mouthing behaviors
		Strabismus
		Hypopigmented skin, light hair, and eye color (compared to family), seen only in patients with 15q11-q13 microdeletion
		Hyperreflexia
		Uplifted, flexed arm position especially during ambulation
		Wide-based gait with lower limb exorotation and ankle valgus
		Increased sensitivity to heat
		Abnormal sleep-wake cycles and reduced total sleep time
		Attraction to/fascination with water; fascination with crinkly objects
		Abnormal food related behaviors
		Obesity (in the older child)
		Scoliosis
		Constipation

(Adapted from Williams et al., 2006.)

In addition to these characteristic rhythmic activities, electroencephalography (EEG) may show epileptic discharges. Interictal nonspecific discharges including spikes, spike-waves, polyspike-wave, and more rarely bursts of fast sharp activity (Cersósimo et al., 2003) may show focal or generalized distribution. A few patients show prolonged runs of 2–3 Hz spike-wave complexes without any clinical correlation (Matsumoto et al., 1992; Dan et al., 2000; Uemura et al., 2005).

Genetic Aspects

In more than 90% of patients with a clinical diagnosis of Angelman syndrome, genetic testing can demonstrate a molecular mechanism causing lack of expression of the *UBE3A* gene. This gene is imprinted in (at least) some brain cells (Rougeulle et al., 1997), being expressed only from the chromosome 15 that is inherited from the mother.

In about 70% of patients with Angelman syndrome, lack of *UBE3A* expression is due to microdeletion of the 15q11-q13 region on the maternally inherited chromosome 15. Similar abnormalities affecting the paternally inherited chromosome 15 result in Prader-Willi syndrome, a clinically distinct condition (Knoll et al., 1989). This illustrates genomic imprinting, where expression of imprinted genes is effectively monoallelic and depends on the paternal or maternal origin. This nonmendelian type of inheritance in human disease also prevails in Huntington disease, Beckwith-Wiedemann syndrome, and Silver-Russell syndrome. Other genes are implicated in the deletion, possibly resulting in a contiguous gene syndrome. The *ATP10C* gene is expressed preferentially from the maternal chromosome only; lack of its expression may underlie eventual obesity (Meguro et al., 2001). ''Pink-eyed dilution'' or *P* gene has been implicated in hypopigmentation that is seen in patients with a 15q11-13 microdeletion, characterized by light skin, reduced retinal pigment, low hair bulb tyrosinase activity, and incomplete melanosome melanization (King et al., 1993). Absence of a copy of the *GABRB3*, *GABRG3,* and *GABRA5* genes, which code for subunits of $GABA_A$ receptor, has tentatively been related to abnormalities in GABAergic neurotransmission (Olsen & Avoli, 1997).

There is a mutation in the maternal *UBE3A* gene (Kishino et al., 1997; Matsuura et al., 1997) in another 5–10% of patients (Malzac et al., 1998; Lossie et al., 2001).

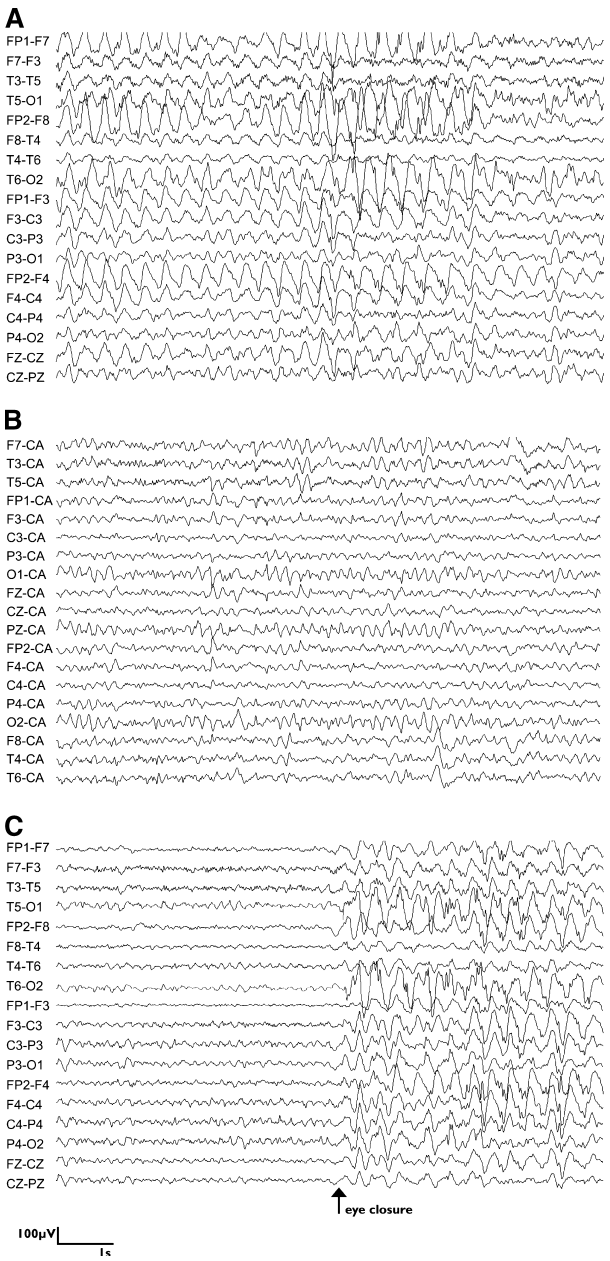

Figure 2.
Typical rhythmic electroencephalographic patterns. **A**. Pattern I: run of high-amplitude delta activity mixed with spikes predominating in the anterior regions without clinical correlation. **B**. Pattern II: run of diffuse moderate-amplitude theta activity (not associated with drowsiness). **C**. Pattern III: high amplitude delta activity mixed with spikes in the posterior regions on eye closure (indexed by the arrow).
Epilepsia © ILAE

About 3–5% of patients have an imprinting defect resulting in lack of the typical maternal pattern of DNA methylation required for *UBE3A* expression (Buiting et al., 1995). Approximately 2–3% of patients inherited both copies of chromosome 15 from the father and none from the mother, that is, paternal uniparental disomy (Malcolm et al., 1991); as a result, no functional copy of the *UBE3A* gene is inherited from the mother. Finally, 1–2% of patients have complex structural chromosome abnormalities leading to inactivation of the maternal *UBE3A* gene (Chan et al., 1993).

To some extent, these molecular categories can be linked to two phenotypic pictures. One is more severe and seen in association with 15q11-q13 microdeletion or *UBE3A* mutation, that is, with only one intact copy of the *UBE3A* gene, which does not bear a maternal methylation pattern. Patients in those groups tend to have more severe microcephaly, greater delay in developmental milestones, more severely impaired communication skills, more severe seizures, and show hypopigmentation (Bürger et al., 1996; Minassian et al., 1998; Moncla et al., 1999; Lossie et al., 2001). The other phenotypic picture is relatively less severe, with low incidence of microcephaly, of hypopigmentation, less severe seizures, and more words, although speech is extremely limited and not used as a main communication tool. It is seen in association with uniparental disomy or imprinting defect, that is, with two intact copies of the *UBE3A* gene, none of which bear a maternal methylation pattern. However, the core phenotypic features, including the rhythmic EEG patterns described earlier, are shared, and there is much overlap in their severity across patients in all molecular classes. Genetic testing, therefore, has confirmatory rather than prognostic value. Nevertheless, obtaining a precise genetic diagnosis is essential in view of the complexity of genetic counseling.

Animal Models

Molecular characterization of Angelman syndrome has allowed the development of animal models of the different mechanisms underlying the syndrome. Such models provide important insights into the pathophysiologic mechanisms involved in various aspects of Angelman syndrome.

A mouse model of maternal microdeletion including the *Ube3a* gene did not result in obvious phenotypic abnormalities, but fine phenotypic aspects, such as motor control, learning skills, or neurophysiological features, have not been studied (Gabriel et al., 1999). This model is potentially very interesting, as it would represent the most prevalent situation in the human condition. The absence of a drastic phenotype, however, contrasts with Angelman syndrome. A model of Angelman syndrome due to paternal uniparental disomy showed high incidence of failure to thrive for the first 4–5 weeks and spontaneous death in the first month (Cattanach et al., 1997). Survivors developed obesity, hyperactive behavior, and gait described as ''ataxic.'' Electrocorticographic recordings showed bilateral prolonged runs of high-amplitude delta rhythmic

activity. The phenotype of proposed models of imprinting defect (Wu et al., 2006) has not been studied in detail, but mice showed a marked decrease in Ube3a (the gene product) in both the cerebral cortex and cerebellum. Mice with selective maternal *Ube3a* gene inactivation, providing models of Angelman syndrome due to maternally-inherited *UBE3A* gene mutation, showed no obvious phenotypic abnormality, but fine testing revealed impaired motor coordination and learning (Jiang et al., 1998; Miura et al., 2002). One of these models showed context-dependent learning impairment and deficits in hippocampal long-term potentiation (Weeber et al., 2003). These abnormalities have been related to diminished calcium/calmodulin–dependent protein kinase II activity, which was secondary to altered autophosphorylation. More recently, van Woerden et al. (2007) demonstrated that loss of this self-inhibition resulted in improvement of both learning defects and synaptic plasticity. This mouse model also showed abnormal dendritic spine development in hippocampal pyramidal neurons (Dindot et al., 2008). Electrocorticographic recordings showed almost continuous runs of rhythmic 3/s activity mixed with polyspikes and slow waves (Jiang et al., 1998). In another mouse model with targeted inactivation of maternal *Ube3a* (Miura et al., 2002), hippocampal electrocorticographic recordings showed runs of high amplitude 4-5/s spike–waves. Intracerebellar recordings in alert mice showed local field potential high frequency (ca. 160 Hz) oscillation correlating with increased Purkinje cell firing rate and rhythmicity (Cheron et al., 2005, 2008).This oscillation was inhibited by gap junction, NMDA, or $GABA_A$ receptor blockers. In sleep, these mice showed reduced proportions of slow-wave sleep (Colas et al., 2005).

Among mouse models that do not involve *Ube3a* expression, the most relevant seems to be provided by mice that are deficient in the *Gabrb3* gene (Homanics et al., 1997). Surviving homozygous knockout mice had seizures, hyperactive behavior, coordination and learning impairment (Homanics et al., 1997; DeLorey et al., 1998), reduced benzodiazepine binding to $GABA_A$ receptors in the cortex (Sinkkonen et al., 2003), and developmental changes in electrocorticographic recordings consisting of progressive slowing and subsequent appearance of high-amplitude irregular slow and sharp waves, and generalized clonic seizures associated with spiking (DeLorey et al., 1998). In vitro electrophysiologic study suggested loss of reciprocal GABAergic inhibition between thalamic reticular neurons (Huntsman et al., 1999). Heterozygotes tended to show behaviors intermediate between wild-type and homozygous null mutants, with significant abnormalities in electrocorticography, seizures, and rest–activity patterns (DeLorey et al., 1998). This model shows interesting similarities with several phenotypic aspects of Angelman syndrome, mostly epilepsy. It has been particularly well studied from the neurophysiologic point of view.

Recently, genetically engineered *Drosophila* with null *Dube3a* (*UBE3A* homolog) has been suggested as a model for Angelman syndrome (Wu et al., 2008). Mutants showed abnormal climbing behavior, impaired olfactory associative memory, and altered free-running circadian activity, which the authors tentatively related (in a somewhat far-fetched leap) with abnormal motor coordination, cognitive impairment, and sleep problems in patients with Angelman syndrome. *Dube3a*-null mutant flies also showed reduced dendritic branching of sensory neurons in the peripheral nervous system and altered growth of terminal dendritic processes (Lu et al., 2009).

Pathophysiology

Although the causative gene was identified more than 12 years ago (Kishino et al., 1997; Matsuura et al., 1997), underlying pathophysiology is still a matter of speculation. The gene product, UBE3A, acts as an E3 ubiquitin–protein ligase along the ubiquitin pathway. The best-characterized function of ubiquitination is to mark target proteins for specific proteolysis by proteasomes. Cytoplasmic accumulation of the p53 oncoprotein was found in Purkinje cells and in a subset of hippocampal neurons maternal *Ube3a*-deficient mice (Jiang et al., 1998). Because this protein is specifically ubiquitinated by UBE3A, the authors suggested that failure of *Ube3a* to ubiquitinate target proteins and promote their degradation could be a key aspect of the pathogenesis of Angelman syndrome. However, these findings have not been replicated in other models. Ubiquitin-mediated proteolysis may be important in a number of neuronal processes, including synaptogenesis and mechanisms of long-term memory. The ubiquitin pathway may also be involved in regulating abundance of postsynaptic receptors (Burbea et al., 2002). Functional absence of UBE3A might thus impair the regulation of $GABA_A$ receptors (Dan & Boyd, 2003). In this hypothesis, altered regulation of $\beta 3$ subunit–containing $GABA_A$ receptors would lead to ''compensation'' involving isoforms of the $GABA_A$ receptor that do not contain the $\beta 3$ subunit, possibly changing the receptors' kinetics and desensitization properties. Although these changes are expected to be subtle, they may have extensive—but yet undocumented—effects during brain maturation as well as through the patient's life. In patients with the common 15q11-q13 microdeletion, hemizygosity of $GABA_A$ receptor subunits $\alpha 5$, $\beta 3$, and $\gamma 3$ has been suggested to underlie deficits in GABA-related neural synchrony mechanisms (Egawa et al., 2008). This could explain the propensity for more severe neurologic impairment in patients with 15q11-q13 microdeletion. Based on data from human patients and animal models, a model of thalamocortical dysfunction resulting from dysregulation of synaptic GABAergic neurotransmission has been proposed to account for the typical rhythmic EEG features

(Dan & Boyd, 2003). In this model, excessive neuronal synchrony precludes the generation complex spontaneous activity in neuronal networks and interferes with neuronal responsiveness. Synchronous network activity disrupts processing of inputs and, therefore, representation of information. Emergence of cerebellar oscillation in maternal *Ube3a*-deficient mice (Cheron et al., 2005) is consistent with a network mechanism implicating gap junctions and $GABA_A$ transmission (Dan et al., 2004; Traub et al., 2008). This oscillation shows similarities with various mouse models with altered calcium signaling (Cheron et al., 2008) and also involves NMDA transmission (Cheron et al., 2005). Hippocampal NMDA-dependent long-term potentiation abnormalities have also been documented in another model with inactivated maternal *Ube3a* (Weeber et al., 2003). In sum, formation of dendritic spines as well as both synaptic (including $GABA_A$ and NMDA transmission) and nonsynaptic (including gap junction) influences appear to be specifically altered in various brain regions (including hippocampus and cerebellar cortex). But much research is still required to fully understand the functional links between lack of *UBE3A* expression and the clinical manifestations of Angelman syndrome.

Perspectives

Despite the gaps that still preclude comprehensive understanding of Angelman syndrome, this condition potentially offers a powerful paradigm for both clinical and basic investigation of the complexity of brain maturation and motor, cognitive, and behavioral development.

One research avenue concerns patient surveys, as exemplified in this issue (Conant et al., 2009; Thibert et al., 2009). Most studies conducted until now have been retrospective and based on questionnaires. Such studies have mostly focused on issues relating to epilepsy, sleep, behavior, communication, or general health. Although large surveys are not expected to provide insights into mechanisms that lead to these manifestations, more studies are still required in these areas in order to add to the current body of knowledge and to refine the notions that have emerged. Given the trend for differences in severity of various phenotypic features between groups of patients from the different molecular classes, it would appear critical to carefully record the underlying genetic cause when constructing cohorts of patients. This might lead to the delineation of a typology of Angelman syndrome with multidimensional classification that could accommodate both milder and more severe atypical phenotypes. Studies of more homogenous categories thus defined would provide much-needed information about the natural history of specific subgroups. They would also make intervention–outcome studies more pertinent. Another key issue that has been overlooked in many previous surveys is the relationship between phenotypic expression and development. It is essential to take the dynamic aspects of development into account. Furthermore, it will become increasingly relevant to gather information about aging in Angelman syndrome. Relevant contextual factors need to be recognized. Quality-of-life issues need to be addressed. This should also encompass the psychological burden on both patients and caregivers, as well as coping strategies. Clinical studies could be considerably enhanced if a carefully designed large-scale database could be set up with open access available to professionals. In this context, cross-study evaluation of various features, and their prevalence and natural history could be performed reliably. This would also allow assessment of the effect of management approaches.

In connection with the neurology of Angelman syndrome, epilepsy has been the most studied subject. Controlled studies of treatment are still very much needed. Other neurologic features would also deserve special attention. With respect to motor control, for example, dysfunctions of various components of the motor system, including the motor cortex, cerebellum, and basal ganglia, have been hypothesized (Dan et al., 2001; Harbord, 2001; Beckung et al., 2004; Dan et al., 2004), but more studies are required to test the hypotheses. It is also important to further investigate cognition. Neuropsychological studies of well-defined subgroups of patients are necessary to shed more light on cognitive processing and learning strategies. This might have implications on the design of appropriate pedagogic approaches. Studies that are more pragmatic are also required, such as those that have assessed training programs (Didden et al., 2001). Almost all electrophysiologic studies conducted to date were limited to EEG, a number of them entertaining confusion between epileptic and nonepileptic changes. Recent methods analyzing brain dynamics and how it modulates neural processing can probably yield invaluable information. The typical rhythmic EEG activities likely reflect dynamic states of neural circuits. Experimental paradigms could be designed to analyze how these network activities are modulated by parameters such as attention or sensory inputs. Evoked-potential techniques (Egawa et al., 2008), and, in particular, ‘‘event-related potentials’’ will likely provide important information on specific aspects of brain functioning. Studies of processing of verbal language will be of special interest. Neuroimaging should also provide more insights into Angelman syndrome (Dan et al., 2009). The recent development of new analysis paradigms of MRI is likely to have implications in the documentation of alternative brain maturation in Angelman syndrome. Functional imaging can address a number of highly relevant issues, also including speech processing. There is also a great need for neuropathologic studies, as only two autopsies have been published.

A large number of current studies concern molecular biology, including investigation of the mechanisms of

imprinting and the possible roles of UBE3A. These studies are extremely important for achieving a better understanding of the involved processes. Based on this understanding, appropriate modulation might be proposed in order to improve neurologic functioning in patients with Angelman syndrome. Molecular biology studies must take into account possible differences between studied species. Among the most pressing questions that are yet to be solved, it will be crucial to discover the functions of UBE3A that are relevant to Angelman syndrome. This might open the way toward possible (partial) compensation for the virtual absence of UBE3A where and when it is needed. However, confusion may arise in association with the use of terms such as ''cure'' to characterize reversal of selected abnormalities in rescue genetically engineered animal models (Elgersma, 2007). ''Cure'' implies recovery from an illness, which is deceptive in this context. Brain development heavily relies on orderly processes that start in the embryo, drawing developmental trajectories. Although the issue of neuronal development has been poorly addressed in Angelman syndrome, it is likely to be altered given documented impairment in neuronal functioning in patients and animal models. Diagnosis is always made relatively late in the brain developmental history: late infancy at best and later childhood in most cases. Current research does not aim at discovering a cure but rather at improving management in order to optimize development, ameliorate symptoms, and improve of quality of life of children and adults with Angelman syndrome. In this context, it is important to consider that the effects of lack of *UBE3A* gene expression may represent an emergent property of developmental interactions among a number of brain regions and functions at the network level rather than a singular, localized dysfunction in otherwise normally developing central nervous system. Given the phenotypic variability even within a molecular class, it may prove important to dedicate attention to individuals' genetic, environmental, and/or developmental context as potential modulating factors.

Another central question concerns the regulation of *UBE3A* gene expression in the hope that it can be enhanced. The phenotypic differences between patients who have one virtually nonfunctional copy of the *UBE3A* gene (i.e., patients with 15q11-q13 microdeletion or *UBE3A* inactivating mutation) and those who have two virtually nonfunctional copies (in case of uniparental disomy or imprinting defect) suggest that there is residual expression when the gene is intact, even in the absence of a functional methylation pattern. Although a dietary supplementation study did not bring about any clear clinical changes (Bacino et al., 2003), more topical intervention might prove useful. Another important question relates to determinants of the deleterious effect of absence of other genes in the 15q11-q13 region. This might explain phenotypic modulation in cases that are caused by a deletion. It might also point to requirements for compensation of lack of gene function. As suggested earlier, the putative roles played by *GABRB3* may prove to be directly relevant to the function of UBE3A.

Some studies concentrate on the possible relationship between genes implicated in Angelman syndrome and other conditions, such as Rett syndrome, autism, or epileptic syndromes. In particular, there seems to be some crucial interactions in the regulation of *MECP2* and *UBE3A* expression (Samaco et al., 2005). There have been recent advances in this domain, which remain controversial (Jordan & Francke, 2006). If the interactions are confirmed, there are likely to be found at multiple levels, perhaps including downstream effects on the regulation of the number of neurons, neuronal and synaptic structure or neurotransmission. Therefore, these interactions would potentially induce fundamental alterations in network properties of the central nervous system. This may also have therapeutic implications.

Finally, we have emphasized active research dedicated to designing animal models of Angelman syndrome. To date, some of these models have not been studied beyond preliminary description. Others, however, have been successfully used for testing hypotheses that might be relevant to human patients.

Conclusion

Although no definite functional links have been established between the genetic abnormalities and the manifestations of Angelman syndrome, a few notions have emerged. First, specific lack of UBE3A production in certain brain cell populations (and perhaps during certain periods in development) is central to the expression of Angelman syndrome. Studies of regulation of *UBE3A* expression are likely to prove extremely important as they may point to possibilities of upregulation in patients. This might include imprinting-related methylation as well as other factors (e.g., regulation of residual activity of unmethylated allele and possible influence of neural activity). Secondly, the main role of UBE3A seems to be exerted through ubiquitination pathways. Studies of different possible effects should be pursued, including putative roles in specific protein degradation, specific intracellular trafficking (e.g., of receptors or other elements implicated in neurotransmission), and possible roles in regulation of transcription. Advances in the understanding of the relevant effects of UBE3A might lead to targeted intervention. Third, different neural ensembles are affected, including cortical networks (with particular emphasis on the hippocampus), thalamocortical networks, and cerebellar networks. These aspects should be documented more extensively, including in a developmental perspective. Fourth, abnormal neuronal functioning is related to excessive rhythmic, synchronous electrophysiologic activities.

These activities likely interfere with physiologic neural processing of information necessary for a number of integrative functions, including cognitive functions, behavioral adaptation, communication, motor control, and some aspects of sleep. Hypersynchrony may also produce epilepsy. Progresses in neuromodulation approaches, including pharmacology, specific stimulation, or inhibition might result in better neurologic function.

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