Behavior and neuropsychiatric manifestations in Angelman syndrome

Karine Pelc¹
Guy Cheron²
Bernard Dan^{1,2}

¹Department of Neurology, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles (ULB), Brussels, Belgium; ²Laboratory of Neurophysiology and Movement Biomechanics, Université Libre de Bruxelles (ULB), Brussels, Belgium

Abstract: Angelman syndrome has been suggested as a disease model of neurogenetic developmental condition with a specific behavioral phenotype. It is due to lack of expression of the *UBE3A* gene, an imprinted gene located on chromosome 15q. Here we review the main features of this phenotype, characterized by happy demeanor with prominent smiling, poorly specific laughing and general exuberance, associated with hypermotor behavior, stereotypies, and reduced behavioral adaptive skills despite proactive social contact. All these phenotypic characteristics are currently difficult to quantify and have been subject to some differences in interpretation. For example, prevalence of autistic disorder is still debated. Many of these features may occur in other syndromic or nonsyndromic forms of severe intellectual disability, but their combination, with particularly prominent laughter and smiling may be specific of Angelman syndrome. Management of problematic behaviors is primarily based on behavioral approaches, though psychoactive medication (eg, neuroleptics or antidepressants) may be required.

Keywords: Angelman syndrome, *UBE3A*, chromosome 15, behavioral phenotypes, autism, neurogenetics

Over the last few decades, the recognition of behavioral phenotypes has become increasingly important in clinical genetics. Behavioral phenotypes have been defined as characteristic patterns of motor, cognitive, communicative and social abnormalities that are consistently associated with a biological disorder (O'Brien and Yule 1995). Being familiar with typical behavioral features as part of manifestations of disease has important implications relating to diagnosis, management and research. From a diagnostic standpoint, identifying a particular behavioral pattern may be as important as recognizing physical dysmorphism. Dykens (1995) suggested that a behavioral phenotype represents increased probability that individuals with a given syndrome exhibit certain behavioral and developmental features in comparison to those who do not present the syndrome. This probabilistic concept of behavioral phenotypes accounts for eventual interindividual variability in occurrence, intensity, and timing of behavioral features.

For diagnostic purposes, it has been recommended that the observed traits should be subjected to assessment using measurable criteria in at least five different domains, namely intellectual functioning, speech and language, attention deficits, social impairment, and other behavioral disturbances (eg, self-injury) (McMahon 1999). Evaluation of the features must take the individuals' developmental complexity into account. It must be noted that there is wide variation in the availability of tests for assessing these different domains. Caution must be taken to avoid restrictive symptom interpretation, which might overlook factors such as anxiety, depression or differently qualified behavioral problems that may be difficult to recognize but might be amenable to effective management.

Correspondence: Bernard Dan
Department of Neurology, Hôpital Universitaire des Enfants Reine Fabiola, Free University of Brussels (ULB), 15 Avenue J.J. Crocq, 1020 Brussels, Belgium
Tel +32 2 477 3174
Fax +32 2 477 2350
Email bernard.dan@ulb.ac.be

As for management, correct identification of certain communication strategies or certain behavioral problems should direct the therapeutic approach while avoiding inappropriate treatment (Pelc and Dan 2008).

As regards research, the concept of behavioral phenotypes has proved to be of great importance for understanding of biological and genetic contributions to behavior. Angelman syndrome provides an historical and on-going illustration of this process. Actually, Harry Angelman (1965) pioneered the behavioral phenotype concept by emphasizing a 'puppet'-like behavior as a distinctive feature of the syndrome he described. Angelman syndrome manifests itself clinically as a severe form of developmental delay including a virtual absence of speech and abnormal gait as well as other coordination difficulties, an exuberant, contagiously happy demeanor with almost constant smiling and prominent laughing, tongue protrusion and a seizure disorder (Table 1).

From a behavioral phenotype to genetic characterization

Replication and extension of Harry Angelman's findings (Angelman 1965) in a large number of patients led to the detection of chromosome 15q abnormalities in a high proportion of cases (Magenis et al 1987). This discovery led to subsequent identification of abnormalities specifically affecting the chromosome 15 inherited from the mother, while similar abnormalities affecting the paternally-inherited are associated with Prader-Willi syndrome, a clinically distinct condition (Knoll et al 1989). These two disorders thus illustrate the phenomenon of genomic imprinting, where the factor determining the phenotypic outcome is the parental origin of the chromosome defect, reflecting differential expression of genes according to their maternal or paternal origin. Angelman syndrome and Prader-Willi syndrome thus provided the first example of 'imprinting mutations' in humans. Therefore, Angelman syndrome has become the clinical archetype of this nonmendelian type of inheritance. Based on the same assumption of the clinical validity of Angelman syndrome, several causative genetic mechanisms were subsequently characterized, eventually leading to the identification of the responsibility of loss of *UBE3A* gene function in inducing the syndrome (Kishino et al 1997; Matsuura et al 1997). Almost all manifestations of Angelman syndrome seem to be related to lack of *UBE3A* gene expression in the brain. In physiological conditions, only the maternal allele is expressed in some brain regions. Lack of *UBE3A* expression may result from several mechanisms including deletion of the 15q11-q13 region of the chromosome 15 inherited from the

mother (this may be isolated or rarely be due to chromosome re-arrangement), paternal uniparental disomy (this may occur postzygotically or less often arise through meiotic nondisjunction), imprinting defect (this may occasionally be due to imprinting center mutation), or *UBE3A* mutation (reviewed in Dan et al 2004a). Because the *UBE3A* gene is known, the characterization of a behavioral phenotype can promote insights into the mechanisms by which they arise. Such a 'bottom-up' line has been suggested for finding the molecular determinants that might account for some neurophysiological aspects of the syndrome (Dan et al 2004b). However, similar approaches aiming to understand genetic mechanisms underlying behavior are likely to be less successful, as contributions of single genes to behavior are very limited. In contrast, interactions between genes, and between genetic and environmental factors are expected to be major. Moreover, further methodological improvements are required to better characterize the behavioral features that accompany the syndrome (Horsler and Oliver 2006b).

Studies of Angelman syndrome behavioral phenotype

The behavioral aspects of a large number of patients with Angelman syndrome have been reported (eg, Robb et al 1989; Fryburg et al 1991; Zori et al 1992; Clayton-Smith 1993; Jolleff and Ryan 1993; Penner et al 1993; Bottani et al 1994; Saitoh et al 1994; Buntinx et al 1995; Bürger et al 1996; Laan et al 1996; Smith et al 1996; Hou et al 1997; Buckley et al 1998; Moncla et al 1999; Dan and Cheron 2003). This has led to preliminary delineation of a constellation of features including prominent laughter, hyperactivity, peculiar communication pattern, mouthing of objects and motor stereotypies. Systematic studies of the behavioral phenotype have confirmed or qualified these observations (Summers et al 1995; Summers and Feldman 1999; Clarke and Marston 2000; Walz and Benson 2002; Oliver et al 2002; Didden et al 2004, 2006; Barry et al 2005; Horsler and Oliver 2006a; Walz 2006). No clear differences have emerged so far between the different molecular classes underlying Angelman syndrome (chromosome 15q11-q13 deletion, uniparental disomy, imprinting defect, or *UBE3A* mutation). The link between genotype and phenotype is yet to be clarified.

Happy demeanor

Apparent happy disposition with frequent smiling and laughing has been regarded as a hallmark of Angelman syndrome since the original description as 'puppet children'

Table 1 Clinical diagnostic criteria for Angelman syndrome (Adapted from Williams et al 2006)**A. Consistent features** (100%)

Developmental delay, functionally severe

Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions

Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotor behavior

Speech impairment, none or minimal use of words; receptive and nonverbal communication skills higher than verbal ones

B. Frequent features (more than 80%)

Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (−2 standard deviations of normal head circumference) by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions

Seizures, onset usually before 3 years of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood

Abnormal electroencephalogram, with a characteristic pattern (Dan and Boyd 2003). The electroencephalographic abnormalities can occur in the first 2 years of life, can precede clinical features, and are often not correlated to clinical seizure events

C. Associated features (20%–80%)

Flat occiput

Occipital groove

Protruding tongue

Tongue thrusting; suck/swallowing disorders

Feeding problems and/or truncal hypotonia during infancy

Prognathia

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 deletion cases

Hyperactive lower extremity deep tendon reflexes

Uplifted, flexed arm position especially during ambulation

Wide-based gait with pronated or valgus-positioned ankles

Increased sensitivity to heat

Abnormal sleep-wake cycles and diminished need for sleep

Attraction to/fascination with water; fascination with crinkly items such as certain papers and plastics

Abnormal food related behaviors

Obesity (in the older child)

Scoliosis

Constipation

(Angelman 1965). It has been reported with great consistency in subsequent descriptions. This aspect served to label the condition ('happy puppet syndrome') for over 15 years, before use of the eponym Angelman syndrome was encouraged (Williams and Frias 1982). It is included within the features of the 'behavioral uniqueness' that characterizes 100% of patients with Angelman syndrome (Williams et al 2006) (Table 1). In a survey of 64 studies reporting behavioral features in a total of 842 patients aged from a few months to 76 years of age, Horsler and Oliver (2006b) noted that only 4 studies did not make any reference to laughing, smiling or happy demeanor. Some authors proposed that smiling and laughing were pathognomonic of the condition (Summers et al 1995). In a comparison with other conditions, individuals with Angelman syndrome were found to be more likely to exhibit cheerful or happy behavior than patients with Down syndrome, Prader-Willi syndrome or nonspecific

mental retardation (Walz and Benson 2002). However, this has been questioned by a more recent case-control study, in which no difference was found in the prevalence of unprovoked laughter between patients with Angelman syndrome and control participants with moderate to profound mental retardation (Barry et al 2005).

Some authors have suggested that bouts of laughter were inappropriate, whether context-inappropriate (eg, Kibel and Burness 1973; Dooley et al 1981; Buntinx et al 1995) or unrelated to context (eg, Berg and Pakula 1972; Elian 1975; Cassidy et al 2000; Lossie et al 2001; Richman et al 2006). It has also been suggested that laughter was independent of happy or sad environments and not associated with any emotional change (Williams and Frias 1982). In our experience, laughter seems to be very often clearly related to context, though it may occur in situations that are not thought to be pleasant, such as blood sampling,

as noted by others (Kibel and Burness 1973; Dooley et al 1981; Clayton-Smith 1992). It may increase markedly with anxiety and some patients may appear to be in discomfort during pervasive bouts of laughter. In the original report, Angelman (1965) described that it could often occur as 'an almost convulsive state' and that 'spike and wave forms were present during the period of laughter'. However, there has been no further evidence of gelastic seizures in Angelman syndrome (Pelc et al 2008a). Extremely rarely, laughing can provoke potentially dangerous syncope (which is amenable to pharmacological treatment) (Vanagt et al 2005). More often smiling and laughing appear to be appropriate. One study specifically addressing this question showed that three children with Angelman syndrome showed increased smiling and laughing in social contexts expressly, contrasting with low levels of smiling and laughing in nonsocial situations (Oliver et al 2002). A further study of 11 children aged 4 to 11 years with a chromosome 15q11-q13 deletion showed that smiling and laughing were enhanced in a condition involving adult speech, touch, smiling, laughing and eye contact compared with a condition involving adult speech only or adult proximity only (Horsler and Oliver 2006a). Laughter may become less frequent with advancing age (Buntinx et al 1995; Laan et al 1996). We have seen several adolescents and adults who looked miserable for prolonged periods; in some cases, this accompanied medical problems such as severe gastroesophageal reflux.

Hyperactivity, impulsivity, and inattention

Hyperactivity has been noted with great consistency (eg, Zori et al 1992; Buntinx et al 1995; Hou et al 1997; Summers and Feldman 1999; Clarke and Marston 2000; Galván-Manso et al 2002; Artigas-Pallarés et al 2005). Hypermotor behavior is mentioned as part of the 'behavioral uniqueness' (Williams et al 2006) (Table 1). Philippart and Minassian (2005) suggested that exuberance better describes this behavior. Lower hyperactivity/noncompliance scores were found than in patients with nonsyndromic developmental disabilities (Summers and Feldman 1999), Smith-Magenis syndrome (Clarke and Marston 2000), or Prader-Willi syndrome (Clarke and Marston 2000). In one other study patients with Angelman syndrome had higher hyperactivity scores than controls with moderate to profound mental retardation (Barry et al 2005). Hyperactivity appears to decrease with age (Buntinx et al 1995; Clarke and Marston 2000). Clayton-Smith (2001) observed that hyperactivity of childhood gave way to reluctance to exercise in all 28 adolescents and adults she studied.

Impulsivity is also frequent. However, it is not more prevalent than in nonspecific mental retardation and significantly less prevalent than in Down syndrome (Walz and Benson 2002). In one study, impulsivity was significantly less frequent in Angelman syndrome (27%) than in nonspecific moderate to profound mental retardation (60%) (Barry et al 2005).

Distractibility and short attention span is frequent but has insufficiently been studied (Hersh et al 1981; Pulsifer 1996; Barry et al 2005). It seems to be comparable with findings in moderate to profound intellectual disability (Barry et al 2005), though one study documented shorter attention span and higher levels of distractibility in Angelman syndrome than Down syndrome, Prader-Willi syndrome, or nonspecific mental retardation (Walz and Benson 2002). Among other factors, attention may be disrupted by seizure activity (Pelc et al 2008b). Attention span has been noted to increase with age (Clayton-Smith 2001).

Effect of management of problematic hyperactivity, impulsivity, and inattention has not been studied in patients with Angelman syndrome. Current approaches are mostly behavioral.

In some patients, neuroleptic (ie, antipsychotic) medication may be beneficial. Low dose neuroleptics (eg, risperidone) may reduce both hyperactivity and impulsivity. Dosage varies according to the desired effect and may greatly differ from patient to patient. Neuroleptics have no significant positive effects on cognitive or attentional problems but may enhance them, particularly at higher doses. They may be associated with a number of side effects, including sedation and motor effects. In addition, propensity toward weight gain may limit the use of risperidone.

Drugs in 'antidepressant' classes may be useful in some patients. In our experience, tricyclic agents, such as amitriptylin, can be effective in reducing hyperactivity and impulsivity. They do not seem to improve attention. Cholinergic side effects may occur, such as dry mouth (which is usually not a problem given the spontaneous drooling) and gastrointestinal perturbations, including constipation. In a few patients, we found that selective serotonin reuptake inhibitors (we used fluoxetine) could reduce hyperactivity, impulsivity and anxiety. However, in one 6 year-old girl with a chromosome 15q11-q13 deletion, fluoxetine seemed to enhance impulsivity, hyperactivity and excitability. Potential interference with sleep quality and architecture (Pelc et al 2008b) should be considered. The recent development of chronobiotic agents may be promising in this respect.

The effectiveness of psychostimulant drugs, such as methylphenidate, has been debated but no sound data are available. In our experience, these agents have not been useful in controlling behavioral problems or in increasing attention in patients with Angelman syndrome. In one personal case (Dan and Boyd 2005), a 7 year-old boy with a chromosome 15q11-q13 deletion, methylphenidate precipitated a state of lethargy associated with generalized fast electroencephalographic activity ('mu rhythm status').

More recent drugs used in attention deficit/hyperactivity disorder, such as atomoxetine, have not been evaluated reliably in Angelman syndrome. In this context, it would appear particularly important to study medication with expected action on mood, anxiety, and attention.

Stereotypies

Stereotyped behaviors, including stereotypies, compulsions, and rituals, can be seen. Motor stereotypies are very frequent (Summers et al 1995; Walz 2006). They may be focal (eg, head shaking, grimacing, bruxism, finger wiggling) or whole-body movements (eg, rocking, jumping, or walking back and forth), with rather fixed and predictable patterns in a given patient. None of these patterns are specific, as they frequently occur in other conditions with mental retardation or communication disorder, and even sometimes in typically developing children.

The most characteristic pattern, mentioned in the clinical diagnostic criteria (Williams et al 2006), is hand flapping and waving. Hand flapping was reported in 73% and 74% of individuals, respectively, in a study of 68 patients (aged 1 to 22 years, mean 9.6) (Artigas-Pallarés et al 2005) and a study of 340 patients (aged 3 to 22 years, mean 11.0) (Walz and Baranek 2006). It must be noted that hand flapping is frequent in other syndromes (eg, fragile X syndrome) as well as nonsyndromic mental retardation and autistic spectrum. Furthermore, stereotyped hand flapping is not uncommon in typically developing infants (Thelen 1979), toddlers and even children (Mahone et al 2004). However, in a comparative study of children and adolescents, patients with Angelman syndrome were found to engage significantly more in repetitive hand flapping than those with Down syndrome, Prader-Willi syndrome or nonspecific mental retardation (Walz and Benson 2002).

Stereotypies also often involve the mouth, with mouthing or chewing of nonedible objects. Prevalence of eating nonfood substances may vary between 5% (Galván-Manso et al 2002) and 42% of patients (Barry et al 2005). This behavior seems to be more prevalent in Angelman syndrome

than in other forms of mental retardation (Walz and Benson 2002).

Occasionally, stereotyped behaviors can have self-injurious effects, such as mouthing blunt objects or toxic substances. Compulsive eye-rubbing, which may become prominent in adolescence or adulthood, may result in keratoconus.

Stress, excitement, fatigue, or apparent boredom may be favoring factors. Stereotypies may be suppressed by distracting the subject. In most individuals, stereotypies do not cause discomfort or significant social impairment. Therefore, no treatment is required. When management is indicated, non-pharmacological approaches appear limited; restrain therapy may lead to discomfort. Pharmacological treatment may also be limited, both by lack of efficacy and adverse effect. Possible options include risperidone and fluoxetine.

Autistic features

In addition to the stereotypies described above, a number of characteristic features of Angelman syndrome may be seen in the context of the autistic spectrum, including virtual absence of speech, impaired use of nonverbal communicative behaviors (facial expression, body postures/gestures to regulate social interaction and decoding of emotional facial expressions), attention deficits, hyperactivity, feeding and sleeping problems, and delays in motor development. Autistic features are considered as comorbidity by some authors (Williams et al 2001) and as characteristic of the syndrome by others. The notion that autistic symptomatology is typical (Steffenburg et al 1996) has been disputed (Thompson and Bolton 2003). Repetitive sensory and motor behaviors have been correlated with a low developmental profile rather than seen as indicating autism (Bonati et al 2007). Several authors have reported a low incidence of autistic features in children with Angelman syndrome (Cohen et al 2005; Veltman et al 2005), emphasizing appropriate social reciprocity (Smith et al 1996; Saitoh et al 1994). In two recent studies, a high incidence of DSM-IV-based diagnoses of autistic disorder was suggested: 10 in 16 (Trillingsgaard and Østergaard 2004) and 8 in 19 (Peters et al 2004a). Three other patients in the first study and all the other patients in the second study had some autistic-like behaviors, most noticeably stereotyped hand or body mannerisms. The discrepancies between the different reports may be related in differences in studied populations and in study design. However, subjective interpretation of the symptomatology might also be an important factor even in studies based on validated evaluation scales. It must be stressed that incorrect diagnosis of autistic spectrum

may result in misinterpretation of behavioral features and in overlooking the social and communication potential. This may enhance the risk of a self-fulfilling prophecy.

Social interaction

In contrast to the autistic-like features, the conviviality of most patients with Angelman syndrome is particularly striking. Interest for social interaction seems to be prominent from early infancy, when social smiling emerges. Most patients are eager to communicate despite the verbal impairment, though nonverbal behaviors, such as facial expressions, body postures, and gestures regulating social interaction, may lack accuracy and be difficult to interpret. The 'happy' disposition is accompanied by a markedly positive interpersonal bias and social disinhibition, which persists in adulthood. Though individuals appear to be almost constantly happy, some may have high levels of anxiety. Fear of strangers is often diminished but specific phobias may be present. Fear of crowds can affect up to half of patients and fear of noise up to a third (Artigas-Pallarés et al 2005). Aggressive behavior is rare both in children and adults (Hersh et al 1981; Zori et al 1992; Summers et al 1995; Clayton-Smith 2001). However, despite a tendency toward social gregariousness and positive interpersonal bias, patients often encounter problems in everyday interaction because of poor detection and respect of emotional and social signals. Therefore, overall social adaptation may be impaired. Management of eventual social maladaptiveness is mostly behavioral. Educational and cultural factors seem to have a major impact on social interaction.

Behavioral adaptability

Adaptive behavior skills are generally reduced, being relatively more impaired than social skills. The impairment in adaptive skills is mostly due to weakness in cognitive (Peters et al 2004b), motor (Dan et al 2001), and communication skills (Jolleff et al 2006). Patients have difficulties in achieving coordinated psychomotor skills and those required for mastering activities of daily living, such as self-help and independence in feeding, dressing and toileting. All individuals require supervision, including as adults. However, there is wide variation in self-help skills. Among 28 patients (16 females and 12 males) aged between 16 and 40 years, 21 were able to walk, 20 could feed themselves, 14 could dress and undress provided the fastenings on the clothes were simple, all required assistance with washing, 20 had day-time sphincter control while 3 had night-time sphincter control, 7 could carry out simple household tasks, most were

able to make simple choices and indicate likes and dislikes but they had no sense of danger, and none were able to cross the street safely on their own or manage money (Clayton-Smith 2001). Three adults in this group had a professional activity (delivering newspapers, cleaning, and helping in a shop), which they carried out under constant supervision. The main problems appear to be difficulties in remaining focused on an activity and impaired recognition of danger. The latter may occasionally be fatal (Ishmael et al 2002). Management with training procedures may be effective for developing adaptive skills (Didden et al 2001).

In contrast with weakness in motor-related skills, patients with Angelman syndrome show a significant strength in socialization (Peters et al 2004b) that is based on nonverbal interactions (Williams et al 2006). This has been hypothesized to be related to happy demeanor (Walz and Benson 2002). However, these authors found that patients with Angelman syndrome did not show higher adaptive social skills than those with nonspecific mental retardation, and significantly less than patients with Down syndrome or Prader-Willi syndrome (Walz and Benson 2002). In general, young adults are described as fitting well into their local communities and as being very sociable (Clayton-Smith 2001). It must be noted that participation in life events and society at large, a dimension that has increasingly been emphasized with respect to disability, is often limited by a form of cultural prescription. The latter may be overcome at many levels. Efforts to increase participation of patients with Angelman syndrome or other disabling conditions should not be less directed at changing environmental factors than at improving adaptive skills.

Eating disorders

In addition to nonfood-related oral behaviors, a variety of eating problems may occur (Clarke and Marston 2000; Williams et al 2006). Increased appetite and behavioral orientation to food affect about a third of patients (Barry et al 2005). These abnormal food behaviors (which are typical of Prader-Willi syndrome) may also lead to obesity (Clayton-Smith 2001). Intensive behavioral approaches may be necessary, including low-calorie diet, a regular exercise regimen, strict enforcement of limits, and constant supervision. Another common food-related problem is marked preference for certain foods, particularly those that do not require much chewing, such as bread, pasta, or banana. Counseling of carers about nutrition and oral function may be helpful. As food preference is a learned behavior, it can be altered by education.

Conclusion

The behavioral phenotype of Angelman syndrome has been increasingly better characterized over the last few decades. Apparent happiness is the hallmark of the syndrome, associated with profuse smiling, poorly specific laughing and general exuberance, with hypermotor behavior, stereotypies, and proactive social contact. However, behavioral adaptation is reduced and this seemingly happy demeanor may be deceptive, in particular with regard to anxiety. Prevalence of autistic disorder is still debated, possibly in relation to discrepancies in interpretation of autistic-like features. Research on animal models has already yielded valuable insights into other features of Angelman syndrome, including some areas of cognition, motor control, epilepsy, sleep, and electrophysiology (Jiang et al 1998; Delorey et al 1998; Miura et al 2002; Weeber et al 2003; Cheron et al 2005, 2008; Colas et al 2005; Handforth et al 2005; van Woerden et al 2007; Ferguson et al 2007). More specific study of behavior is still needed. In addition, the study of these behavioral aspects poses specific problems, some of which can only be addressed by studying the patients directly. This should be performed using approaches designed to decipher the complexity of human behavior in the setting of severe intellectual disability (Horsler and Oliver 2006b). Currently, management of problematic behaviors in patients with Angelman syndrome is primarily based on behavioral approaches, but psychoactive medication (eg, neuroleptics or antidepressants) may be required. Coping strategies of caregivers often need to be reinforced by counseling.

References

- Angelman H. 1965. 'Puppet' children: A report on three cases. *Dev Med Child Neurol*, 7:681–8.
- Artigas-Pallarés J, Brun-Gasca C, Gabau-Vila E, Guitart-Feliubadaló M, Camprubí-Sánchez C. 2005. Aspectos médicos y conductuales del síndrome de Angelman. *Rev Neurol (Madrid)* 41:649–56.
- Barry RJ, Leitner RP, Clarke AR, et al. 2005. Behavioral aspects of Angelman syndrome: a case control study. *Am J Med Genet* 132:8–12.
- Berg JM, Pakula Z. 1972. Angelman's ("happy puppet") syndrome. *Am J Dis Child*, 123:72–4.
- Bonati MT, Russo S, Finelli P, et al. 2007. Evaluation of autism traits in Angelman syndrome: a resource to unfold autism genes. *Neurogenetics*, 8:169–78.
- Bottani A, Robinson WP, DeLozier-Blanchet CD, et al. 1994. Angelman syndrome due to parental uniparental disomy of chromosome 15: a milder phenotype? *Am J Med Genet*, 51:35–40.
- Buckley RH, Dinno N, Weber P. 1998. Angelman syndrome: are the estimates too low? *Am J Med Genet*, 80:385–90.
- Buntinx IM, Hennekam RCM, Brouwer OF, et al. 1995. Clinical profile of Angelman syndrome at different ages. *Am J Med Genet*, 56:176–83.
- Bürger J, Kunze J, Sperling K, et al. 1996. Phenotypic differences in Angelman syndrome patients: imprinting mutations show less frequently microcephaly and hypopigmentation than deletions. *Am J Med Genet*, 66:221–6.
- Cassidy SB, Dykens E, Williams CA. 2000. Prader-Willi and Angelman Syndromes: sister imprinted disorders. *Am J Med Genet*, 97:136–46.
- Cheron G, Servais L, Wagstaff J, et al. 2005. Fast cerebellar oscillation associated with ataxia in a mouse model of Angelman syndrome. *Neuroscience*, 130:631–7.
- Cheron G, Servais L, Dan B. 2008. Cerebellar network plasticity: from genes to fast oscillation. *Neuroscience*, in press.
- Clarke DJ, Marston G. Problem behaviors associated with 15q- Angelman syndrome. 2000. *Am J Ment Retard*, 105:25–31.
- Clayton-Smith J. 1992. Angelman's syndrome. *Arch Dis Child*, 67:889–91.
- Clayton-Smith J. 1993. Clinical research on Angelman syndrome in the United Kingdom: observations on 82 affected individuals. *Am J Med Genet*, 46:12–15.
- Clayton-Smith J. 2001. Angelman syndrome: evolution of the phenotype in adolescents and adults. *Dev Med Child Neurol*, 43:476–80.
- Cohen D, Pichard N, Tordjman S, et al. 2005. Specific genetic disorders and autism: clinical contribution towards their identification. *J Autism Dev Disord*, 35:103–16.
- Colas D, Wagstaff J, Fort P, et al. 2005. Sleep disturbances in *Ube3a* maternal-deficient mice modeling Angelman syndrome. *Neurobiol Dis*, 20:471–48.
- Dan B, Boyd SG. 2003. Angelman syndrome reviewed from a neurophysiological perspective. The *UBE3A-GABRB3* hypothesis. *Neuropediatrics*, 34:169–76.
- Dan B, Boyd SG. 2005. Nonconvulsive (dialeptic) status epilepticus in children. *Curr Pediatr Rev*, 1:7–16.
- Dan B, Cheron G. 2003. Le syndrome d'Angelman syndrome: un modèle clinique et génétique. *Rev Neurol (Paris)*, 159:499–510.
- Dan B, Bouillot E, Bengoetxea A, et al. 2001. Distinct multi-joint control strategies in spastic diplegia associated with prematurity or Angelman syndrome. *Clin Neurophysiol*, 112:1618–25.
- Dan B, Boyd SG, Cheron G. 2004a. From genomic imprinting to developmental physiology: identifying stepping stones. *Curr Pharmacogenomics*, 2:232–43.
- Dan B, Servais L, Boyd SG, et al. 2004b. From electrophysiology to chromatin: a bottom-up approach to Angelman syndrome. *Ann N Y Acad Sci*, 1030:599–611.
- DeLoey TM, Handforth A, Anagnostaras SG, et al. 1998. Mice lacking the beta3 subunit of the GABA_A receptor have the epilepsy phenotype and many of the behavioral characteristics of Angelman syndrome. *J Neurosci*, 18:8505–14.
- Didden R, Sikkema SPE, Bosman ITM, et al. 2001. Use of a modified Azrin-Fox toilet training procedure with individuals with Angelman syndrome. *J Appl Res Intellect Dis*, 14:64–70.
- Didden R, Korzilius H, Duker P, et al. 2004. Communicative functioning in individuals with Angelman syndrome: a comparative study. *Disabil Rehabil*, 26:1263–7.
- Didden R, Korzilius H, Kamphuis A, et al. 2006. Preferences in individuals with Angelman syndrome assessed by a modified Choice Assessment Scale. *J Intellect Disabil Res*, 50:54–60.
- Dooley JM, Berg JM, Pakula Z, et al. 1981. The puppet-like syndrome of Angelman. *Am J Dis Child*, 135:621–4.
- Dykens E. 1995. Measuring behavioral phenotypes: provocations from the 'New Genetics'. *Am J Med Genet*, 99:522–32.
- Elian M. 1975. Fourteen happy puppets. *Clin Pediatr (Phila)*, 14:902–8.
- Ferguson C, Hardy SL, Werner DF, et al. 2007. New insight into the role of the beta3 subunit of the GABAA-R in development, behavior, body weight regulation, and anesthesia revealed by conditional gene knock-out. *BMC Neurosci*, 8:85.
- Fryburg JS, Breg WR, Lindgren V. 1991. Diagnosis of Angelman syndrome in infants. *Am J Med Genet*, 38:58–64.
- Handforth A, Delorey TM, Homanics GE, et al. 2005. Pharmacologic evidence for abnormal thalamocortical functioning in GABA receptor $\beta 3$ subunit-deficient mice, a model of Angelman syndrome. *Epilepsia*, 46:1860–70.
- Horsler K, Oliver C. 2006a. Environmental influences on the behavioral phenotype of Angelman syndrome. *Am J Ment Retard*, 111:311–21.

- Horsler K, Oliver C. 2006b. The behavioural phenotype of Angelman syndrome. *J Intellect Disabil Res*, 50:33–53.
- Hou JW, Wang PJ, Wang TR. 1997. Angelman syndrome assessed by neurological and molecular cytogenetic investigations. *Pediatr Neurol*, 16:17–22.
- Ishmael HA, Begleiter ML, Butler MG. 2002. Drowning as a cause of death in Angelman syndrome. *Am J Ment Retard*, 107:69–70.
- Jiang YH, Armstrong D, Albrecht U, et al. 1998. Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. *Neuron*, 21:799–811.
- Jolleff N, Ryan M. 1993. Communication development in Angelman's syndrome. *Arch Dis Child*, 69:148–58.
- Jolleff N, Emmerson F, Ryan M, et al. 2006. Communication skills in Angelman syndrome: Matching phenotype to genotype. *Adv Speech Lang Pathology*, 8:28–33.
- Kibel MA, Burness FR. 1973. The 'Happy Puppet' syndrome. *Centr Afr J Med*, 19:91–3.
- Kishino T, Lalonde M, Wagstaff J. 1997. *UBE3A/E6-AP* mutations cause Angelman syndrome. *Nat Genet*, 15:70–3.
- Knoll JH, Nicholls RD, Magenis RE, et al. 1989. Angelman and Prader-Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion. *Am J Med Genet*, 32:285–90.
- Laan LAEM, den Boer ATH, Hennekam RCM, et al. 1996. Angelman syndrome in adulthood. *Am J Med Genet*, 66:356–60.
- Lossie AC, Whitney MM, Amidon D, et al. 2001. Distinct phenotypes distinguish the molecular classes of Angelman syndrome. *J Med Genet*, 38:834–45.
- Magenis RE, Brown MG, Lacy DA, et al. 1987. Is Angelman syndrome an alternate result of del(15)(q11q13)? *Am J Med Genet*, 28:829–38.
- Mahone EM, Bridges D, Prahme C, et al. 2004. Repetitive arm and hand movements (complex motor stereotypies) in children. *J Pediatr*, 145:391–5.
- Matsuura T, Sutcliffe JS, Fang P, et al. 2007. *De novo* truncating mutations in E6-AP ubiquitin-protein ligase gene (*UBE3A*) in Angelman syndrome. *Nat Genet*, 15:74–7.
- Hersh JH, Bloom AS, Zimmerman AW, et al. 1981. Behavioral correlates in the happy puppet syndrome: a characteristic profile? *Dev Med Child Neurol*, 23:792–800.
- Galván-Manso M, Campistol J, Monros E, et al. 2002. Síndrome de Angelman: características físicas y fenotipo conductual en 37 pacientes con diagnóstico genético confirmado. *Rev Neurol (Madrid)*, 35:425–9.
- McMahon W. 1999. Advances in the cognitive neuroscience of neurodevelopmental disorders: Views from child psychiatry and medical genetics. In: Tager-Flusberg H (ed). *Neurodevelopmental Disorders*. Cambridge, MA: MIT Pr, pp. 583–600.
- Miura K, Kishino T, Li E, et al. 2002. Neurobehavioral and electroencephalographic abnormalities in Ube3a maternal-deficient mice. *Neurobiol Dis*, 9:149–59.
- Moncla A, Malzac P, Voelckel MA, et al. 1999. Phenotype-genotype correlation in 20 deletion and 20 nondeletion Angelman syndrome patients. *Eur J Hum Genet*, 7:131–9.
- O'Brien G, Yule W. 1995. *Behavioural Phenotypes*. London: Mac Keith Press.
- Oliver C, Demeetriades L, Hall S. 2002. Effects of environmental events on smiling and laughing behavior in Angelman syndrome. *Am J Ment Retard*, 107:194–200.
- Pelc K, Dan B. 2008. The ADHD Tetragrammaton taken in vain in neuro-genetic disorders? *Acta Paediatr*, 1:2–4.
- Pelc K, Boyd SG, Cheron G, et al. 2008a. Epilepsy in Angelman syndrome. *Seizure*, in press.
- Pelc K, Cheron G, Boyd SG, et al. 2008b. Are there distinctive sleep problems in Angelman syndrome? *Sleep Med*, in press.
- Penner KA, Johnston J, Faircloth BH, et al. 1993. Communication, cognition and social interaction in the Angelman Syndrome. *Am J Med Genet*, 46:34–9.
- Peters SU, Beaudet AL, Madduri N, et al. 2004a. Autism in Angelman's syndrome: implications for autism research. *Clin Genet*, 66:530–6.
- Peters SU, Goddard-Finegold J, Beaudet AL, et al. 2004b. Cognitive and adaptive behavior profiles of children with Angelman syndrome. *Am J Med Genet*, 128:110–13.
- Philippart M, Minassian BA. 2005. Angelman syndrome from infancy to old age [abstract]. *Am J Hum Genet*, 79(Suppl):605.
- Pulsifer MB. 1996. The neuropsychology of mental retardation. *J Int Neuropsychol Soc*, 2:159–76.
- Richman DM, Gernat E, Teichman H. 2006. Effects of social stimuli on laughing and smiling in young children with Angelman syndrome. *Am J Ment Retard*, 111:442–6.
- Robb SA, Pohl KRE, Baraister M, et al. 1989. The 'happy puppet' syndrome of Angelman: review of the clinical features. *Arch Dis Child*, 64:83–6.
- Saitoh S, Harada N, Jinno Y, et al. 1994. Molecular and clinical study of 61 Angelman syndrome patients. *Am J Med Genet*, 52:158–63.
- Smith A, Wiles C, Haan E, et al. 1996. Clinical features in 27 patients with Angelman syndrome resulting from DNA deletion. *J Med Genet*, 33:107–12.
- Steffenburg S, Gillberg CL, Steffenburg U, et al. 1996. Autism in Angelman syndrome: a population-based study. *Pediatr Neurol*, 14:131–6.
- Summers JA, Feldman MA. 1999. Distinctive pattern of behavioural functioning in Angelman syndrome. *Am J Ment Retard*, 104:376–84.
- Summers JA, Allison DB, Lynch PS, et al. 1995. Behaviour problems in Angelman syndrome. *J Intellect Disabil Res*, 39:97–106.
- Thelen E. 1979. Rhythmical stereotypies in normal human infants. *Animal Behav*, 27:699–715.
- Thompson RJ, Bolton PF. 2003. Case report: Angelman syndrome in an individual with a small SMC(15) and paternal uniparental disomy: a case report with reference to the assessment of cognitive functioning and autistic symptomatology. *J Autism Dev Disord*, 33:171–6.
- Trillingsgaard A, Østergaard JR. 2004. Autism in Angelman syndrome: An exploration of comorbidity. *Autism*, 8:163–74.
- Vanagt WY, Pulles-Heintzberger CF, Vernoooy K, et al. 2005. Asystole during outbursts of laughing in a child with Angelman syndrome. *Pediatr Cardiol*, 26:866–8.
- van Woerden GM, Harris KD, Hojjati MR, et al. 2007. Rescue of neurological deficits in a mouse model for Angelman syndrome by reduction of alphaCaMKII inhibitory phosphorylation. *Nat Neurosci*, 10:280–2.
- Veltman MWM, Craig EE, Bolton P. 2005. Autism spectrum disorders in Prader-Willi and Angelman syndromes: a systematic review. *Psychiatric Genetics*, 15:243–54.
- Walz NC. 2006. Parent report of stereotyped behaviors, social interaction, and developmental disturbances in individuals with Angelman syndrome. *J Autism Dev Disord*, 37:940–7.
- Walz NC, Baranek GT. 2006. Sensory processing patterns in persons with Angelman syndrome. *Am J Occup Ther*, 60:472–9.
- Walz NC, Benson BA. 2002. Behavioral phenotypes in children with Down syndrome, Prader-Willi syndrome, and Angelman syndrome. *J Dev Phys Disabil*, 14:307–21.
- Weeber EJ, Jiang YH, Elgersma Y, et al. 2003. Derangements of hippocampal calcium/calmodulin-dependent protein kinase II in a mouse model for Angelman mental retardation syndrome. *J Neurosci*, 23:2634–44.
- Williams CA, Frias JL. 1982. The Angelman ("happy puppet") syndrome. *Am J Med Genet*, 11:453–60.
- Williams CA, Lossie A, Driscoll D, et al. 2001. Angelman syndrome: mimicking conditions and phenotypes. *Am J Med Genet*, 101:59–64.
- Williams CA, Beaudet AL, Clayton-Smith J, et al. 2006. Angelman syndrome 2005: updated consensus for diagnostic criteria. *Am J Med Genet*, 140:413–18.
- Zori RT, Hendrickson J, Woolven S, et al. 1992. Angelman syndrome: clinical profile. *J Child Neurol*, 7:270–80.