American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 154C:448–455 (2010)

ARTICLE

The Behavioral Phenotype of the Idic(15) Syndrome

AGATINO BATTAGLIA,* BARBARA PARRINI, AND RAFFAELLA TANCREDI

Idic(15) syndrome is a neurogenetic disorder clinically delineated by early central hypotonia, developmental delay and intellectual disability (ID), epilepsy, absent or very poor speech, and autistic or autistic-like behavior. It is due to the presence of a supernumerary marker chromosome formed by the inverted duplication of proximal chromosome 15, resulting in tetrasomy 15p and partial tetrasomy 15q, and containing the Prader–Willi/Angelman syndrome critical region (PWS/ASCR). The vast majority of these idic(15) derives from the two homologous maternal chromosomes at meiosis. To better define the behavior profile, we studied 22 idic(15) children (15 males and 7 females) observed at our institute between 1986 and 2010, and present, in detail, case studies of five of them. We have been able to perform standardized and semi-standardized measures of intelligence, and psychopathology in only 13 of our 22 patients, due to the limitations of chronological age, and to the severity of ID (ranging from mild–moderate, in 15%, to severe–profound, in 85% of our sample). The results show a distinct developmental profile in idic(15) patients, that may provide a behavioral signature for autism spectrum disorder (ASD)/ASD-like arising from the susceptibility locus on proximal 15q; and suggest that idic(15) individuals are not ''true autistic,'' but distinct ''autistic-like'' persons with high score in the third ADOS-G and ADI-R area.

KEY WORDS: idic (15) syndrome; inv dup(15) syndrome; supernumerary marker chromosome 15; behavior phenotype; autism; PDD; ASD

How to cite this article: Battaglia A, Parrini B, Tancredi R. 2010. The Behavioral Phenotype of the idic(15) Syndrome. Am J Med Genet Part C 154C:448–455.

INTRODUCTION

The chromosome region 15q11q13 is prone to genomic rearrangements, due to the presence of repeated DNA elements [Christian et al., 1999; Makoff and Flomen, 2007]. Many rearrangements may occur in this imprinted segment of a ~6 Mb unit, defined by proximal breakpoints BP1 or BP2 and distal breakpoint BP3 [Roberts et al., 2003]: deletions associated either with Angelman syndrome (AS) or with Prader–Willi syndrome (PWS), according to parental origin [Lalande, 1996]; translocations; inversions; and supernumerary marker chromosomes formed by the inverted duplication of proximal chromosome 15. Interstitial duplications, triplications, and balanced reciprocal translocations are much less frequent [Browne et al., 1997]. The inv dup (15) is the most common of the heterogeneous group of the extra structurally abnormal chromosomes (ESACs). Most ESACs(15) are bisatellited and dicentric, containing varying amounts of 15q material between the two centromeres.

Two cytogenetic types of inv dup (15) or idic(15) marker chromosomes have been identified, that have different phenotypic consequences [Maraschio et al., 1988; Leana-Cox et al., 1994; Crolla et al., 1995; Huang et al., 1997].

Two cytogenetic types of inv dup (15) or idic(15) marker chromosomes have been identified, that have different phenotypic consequences.

Dr. Agatino Battaglia is Contract Professor of Child Neuropsychiatry at the Postgraduate Medical School, University of Pisa, Italy; and Adjunct Professor of Pediatrics at the University of Utah Health Sciences Center, Division of Medical Genetics, Department of Pediatrics, Salt Lake City, UT, USA. He is board certified in Clinical Pediatrics and in Neurology. He is Director of the Clinical Dysmorphology Unit, Head of the Center for the Study of Congenital Malformation Syndromes, and Director of Research in Neuropsychiatric Genetics at the Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, Calambrone (Pisa), Italy. He is Associate Editor of the American Journal of Medical Genetics. He has a strong research interest in clinical dysmorphology, neuropsychiatric genetics, and clinical neurophysiology.

Dr. Barbara Parrini is a Psychologist working at the Stella Maris Clinical Research Institute for Child and Adolescent Neuropsychiatry, Calambrone (Pisa), Italy. She has strong research interests in the neuropsychological and behavioural profiles of individuals with chromosomal and pervasive developmental disorders.

Dr. Raffaella Tancredi is a Child Neuropsychiatrist, and Psychoanalyst, working at The Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, Calambrone (Pisa), Italy. She is Contract Professor of Child Neuropsychiatry at the Post-Graduate Medical School in Child Neuropsychiatry, University of Pisa; and has strong research interests in the clinics of pervasive developmental disorders. She has contributed to the Italian version of ADIR and ADOS.

*Correspondence to: Agatino Battaglia, M.D., Stella Maris Clinical Research Institute for Child and Adolescent Neuropsychiatry, Via dei Giacinti, 2—56128 Calambrone, Pisa, Italy. E-mail: agatino.battaglia@inpe.unipi.it

DOI 10.1002/ajmg.c.30281

Published online 25 October 2010 in Wiley Online Library (wileyonlinelibrary.com).

One is a metacentric or submetacentric and heterochromatic chromosome, smaller or similar to a G group chromosome, not containing the PWS/AS critical region (PWS/ASCR), and the cytogenetic description is dic(15)(q11). Most children with this aberration show a normal phenotype [Cheng et al., 1994], although exceptions have been observed [Hou and Wang, 1998]. The second type of idic (15) is as large as, or larger than, a G group chromosome and has 15q euchromatin. It includes the PWS/ASCR [Robinson et al., 1993; Blennow et al., 1995], and the cytogenetic description is dic(15)(q12 or q13). The vast majority of dic(15)(q12 or q13) derives from the two homologous maternal chromosomes at meiosis, and is said to be associated with increased mean maternal age at conception, similar to other trisomies. This implies that a duplication of the paternal PWS/ASCR is either a rare event, has a lethal effect, or goes undetected due to the absence of phenotypic expression [Maraschio et al., 1988]. The presence of large idic(15) results in tetrasomy 15p and partial tetrasomy 15q. However, considerable structure heterogeneity has recently been reported [Wang et al., 2008]. The large idic(15) are nearly always sporadic, and are associated with an abnormal phenotype, which constitutes the idic(15) syndrome [Flejter et al., 1996; Battaglia et al., 1997]. Maternally derived cytogenetic mosaicism with a normal cell line has been described in a small subset of individuals [Crolla et al., 2005; Loitzsch and Bartsch 2006]; and a patient with a mosaic paternally derived idic(15), showing a mild PWS phenotype, has also been observed [Saitoh et al., 2007].

Idic(15) syndrome is reportedly characterized by a distinct neurobehavioral phenotype including moderate to profound developmental delay/intellectual disability (ID), absent or very poor speech, hypotonia, epilepsy, and an autism spectrum disorder (ASD) [Gillberg et al., 1991; Robinson et al., 1993; Webb, 1994; Crolla et al., 1995; Battaglia et al., 1997; Webb et al., 1998; Battaglia, 2005]. Incidence at birth is estimated to be 1/30,000 with a sex ratio of almost 1 [Schinzel and Niedrist, 2001]. However, this is probably an underestimation, due to the difficulty in making the clinical diagnosis for the absence of malformations or of overt craniofacial dysmorphisms, in most individuals. Standard cytogenetics must be associated with FISH analysis, using probes both from proximal chromosome 15 and from the PWS/ASCR [Luke et al., 1994; Webb et al., 1998]. Molecular studies, such as microsatellite analysis on parental DNA or methylation analysis on the proband DNA, are also needed in order to detect the parent-of-origin of the idic(15) chromosome [Luke et al., 1994; Webb et al., 1998]. Array comparative genomic hybridization (array-CGH) has been shown to be useful for the detection of both the duplication and its extent, and atypical forms of idic(15) [Wang et al., 2004, 2008].

Genotype/phenotype studies have not been able, to date, to show any correlation between type and size of the idic(15), and the degree of severity of the clinical spectrum.

The initial observation by Battaglia et al. [1997] of a behavior disorder characterized by autistic features has withstood the test of time, and this behavior, associated with severe epilepsy, and ID makes idic(15) syndrome one of the prototypic genetic syndromes having a neurobehavioral phenotype. The purpose of this article is to more clearly describe the distinctive behavior of idic(15) individuals.

The initial observation by Battaglia et al. of a behavior disorder characterized by autistic features has withstood the test of time, and this behavior, associated with severe epilepsy, and ID makes idic(15) syndrome one of the prototypic genetic syndromes having a neurobehavioral phenotype. The purpose of this article is to more clearly describe the distinctive behavior of idic(15) individuals.

CLINICAL VERSUS BEHAVIORAL PHENOTYPE

The main features defining the clinical phenotype have been previously published [Cheng et al., 1994; Leana-Cox et al., 1994; Blennow et al., 1995; Battaglia et al., 1997; Dennis et al., 2006; Battaglia, 2008]. They consist of severe developmental delay/ID, speech impairment, epilepsy, and altered behavior.

While severe developmental delay/ID and marked speech impairment are seen in a variety of genetic syndromes, hard-to-control epilepsy begins to confer some specificity on these core features. The combination of severe epilepsy and the particular behavior disorder renders a more distinctive clinical picture that begins to distinguish idic(15) syndrome from other conditions involving severe neurodevelopmental disability.

The combination of severe epilepsy and the particular behavior disorder renders a more distinctive clinical picture that begins to distinguish idic(15) syndrome from other conditions involving severe neurodevelopmental disability.

The first evidence of the distinctive behavior of idic(15) syndrome may become apparent very early in life. A few infants may smile to their own mother for a short time, but soon loose eye-to-eye contact, and do not develop appropriate social interaction. Most children use to call for food by crying, and prefer being left alone. They are

withdrawn from early on, and do not show interest toward their peers. Language remains very poor, often echolalic. Comprehension is very limited, contextual, and accompanied by the gesture. The majority does not acquire social imitative play. Stereotyped movements, such as turning themselves around and repetitive hand-twisting, can be observed in childhood. Intention to communicate is absent or very poor early in life.

To better describe the distinctive behavior of idic(15) individuals, we are presenting the case histories of 5 out of 22 idic(15) patients observed at our institute between 1986 and 2010.

Due to the limitations of chronological age, and to the severity of ID (ranging from mild–moderate, in 15%, to severe–profound, in 85% of our sample), we have been able to perform standardized and semi-standardized measures of intelligence (Griffiths, Leiter, Uzgiris-Hunt, Vineland Adaptive Behavior Scale (VABS)—Survey Form, chosen according to the child's adaptive abilities) and psychopathology (ADI-R, ADOS-G, CARS), in only 13 of our 22 patients. Due to the aforementioned limitations, we obtained reliable diagnostic results in only 6 (5/6 are described in detail herein) out of 13.

CLINICAL REPORTS

Patient 1

Patient 1 is a 14-year-old boy with idic(15) syndrome who was born in 1996. Firstly, we had seen him at age 8 years for developmental delay and poor speech. He was born at term, by normal delivery, after an uneventful pregnancy. Apgar was reportedly 8 and 10. He was breast fed with valid suction. Marked, diffuse hypotonia was soon observed. He held his head at 8 months, sat with no support at 15 months, and walked independently at 18 months. He pronounced his first words at age 3 years, and comprehension was contextual. He was withdrawn from early on, showing no interest toward his peers, being very passive, with no eye-to-eye contact. He never achieved sphincter control. When firstly evaluated by us, at age 8 years, he had a severe ID (IQ 25); was able to pronounce a few words spontaneously in keeping with the context; and, on occasions, was able to pronounce some words or simple sentences in immediate echolalia. Gesture repertoire was poor. When requested to do something, he used to respond with the prosthetic use of the adult, not associated with eye contact. He had a poor eye-to-eye contact, with a reduced mimic expressivity. A smile could be seen in pleasant situations, but not toward the other. There were no behaviors such as showing or drawing attention of the other to share attention, pleasure, or enjoyment. He showed selective interest toward some objects, particularly small cars, from which was difficult to dissuade and with which repetitive patterns of behavior were observed (pushing them back and forth) together with a bizarre use of vision (observing the wheels too closely, with the periphery of the eyes). Other objects were explored through sensorimotor patterns (liking and/or smelling them). No imitative play was ever observed. Height was 120 cm (50th centile), weight 38.5 kg (>97th centile), and OFC 51 cm (2nd–50th centile). Mildly downslanting palpebral fissures, highly arched palate, hypotonic face with drooling, diffuse marked hypotonia, joint hyperextensibility, and abdomen adiposity were noted. He showed an aimless hyperactivity, with oppositional behavior. When thwarted, he reacted with aggressiveness. The VABS [Sparrow et al., 1984] domain scores were 20 (<1.6 years age equivalent) in the communication, 28 (1.6 years age equivalent) in daily living skills, and 27 (<1.6 years age equivalent) in socialization. The Child Autism Rating Scale (CARS) showed a score of 42, consistent with severe autism. ADOS-G Module 1 (Pre-Verbal/Single Words) [Lord et al., 2002] gave the following scores: Social Interaction Total 11 (autism cut-off = 7); Communication Total 6 (autism cut-off = 4); Total Score 17 (autism cut off = 12) confirming a diagnosis of autism. Besides, the third area (stereotyped behaviors and restricted interests) score was 3.

At 11 years he had his first generalized epileptic seizure, during sleep, followed by other episodes, treated with sodium valproate, rufinamide, and clobazam with good control.

Over time, he has shown a slow, but global evolution of the adaptive behavior, and social interaction, with an improvement in the communicative skills (mainly directed at his own needs) and verbal comprehension, and some decreased occurrence of withdrawal behavior.

At present, aged 14 years, he still does not have any sphincter control; is still hyperactive, but he's able to help with simple household tasks, such as setting the table for breakfast, shut windows and doors, and throw away trash. His school plan includes a specific program to improve his social interaction, and his tolerance to frustrations.

Patient 2

Patient 2 is a 16-year-old boy with idic(15) syndrome who was born in 1994. Firstly, we had seen him at age 2½ years for developmental delay and withdrawal behavior. He was the forth child of healthy non-consanguineous parents, born at term, by normal delivery, after an uneventful pregnancy. Family history was non-contributory. His prenatal and immediately postnatal periods were unremarkable. However, psychomotor delay was obvious early. Diffuse hypotonia was soon observed. He held his head at 5 months, sat with no support at 11 months, and walked independently at 18 months. He pronounced his first words at age 3 years, and comprehension was contextual. He was withdrawn from early on, showing no interest toward his peers, being very passive, with no eye-to-eye contact. He never achieved sphincter control. Since age 2½ years, he has been followed up by us on a regular basis. He has a severe ID (IQ 30); is able to pronounce simple sentences spontaneously in keeping with the context; comprehension is very limited and contextual. At 6 years 9 months, he had his first generalized epileptic seizures (atypical absences), followed by tonic seizures mainly occur-

ring during sleep, and by generalized tonic-clonic fits. These were treated and partly controlled with sodium valproate, carbamazepine, and lamotrigine. The above seizures associated with an abnormal EEG, showing distinct diffuse and multifocal discharges, were in keeping with a Lennox–Gastaut-like epileptic syndrome.

He had pubarche at age 10 years. ADOS-G Module 2 (Phrase Speech) [Lord et al., 2002] gave the following scores: Social Interaction Total 5 (autism cut-off = 6; autism spectrum cut-off = 4); Communication Total 6 (autism cut-off = 5); Total score 11 (autism cut off = 12; autism spectrum cut-off = 8) consistent with a diagnosis of autism spectrum. Besides, the third area (stereotyped behaviors and restricted interests) score was 2.

ADI-R [Lord et al., 1994] gave the following scores: qualitative compromission of social interaction 15 (cut-off = 10), communication 7 (cut-off = 8), repetitive behaviors and stereotyped patterns 6 (cut-off = 3), not consistent with a diagnosis of autism. The CARS showed a score of 30 (cut-off for autism = 30). At age 15 years 2 months, he was admitted as an emergency to the psychiatric ward of our institute, due to worsening of his oppositional-defiant behavior associated with a mood disorder (a probable bipolar disorder-NOS). Reportedly, his defiant behavior had started at 13 years, particularly toward his father, at times, associated with aggressiveness. By the same time, he started annoying his peers at school, with defiant and exhibitionistic conducts; bouts of hyperactivity, and actively defying and refusing to comply with teachers' requests and rules. Day by day he appeared more verbally aggressive toward his father; with an increase of the oppositional defiant behavior leading both to aggressive verbalizations and conducts. Such a behavior had also been observed within the school and the rehabilitation context. By the same time, there had been an increase in his sexual conducts, directed at female figures, with research of physical contact and tendency to strip himself in public. He showed an excessive use of his language, with deferred echolalia, not always contextual (confabulation), and stereotypies. When faced with simple requests, he showed marked anxiety with a behavioral disorganization. He had difficulty with task planning and supervision, with a marked attention deficit. After family interview, it was clear that the oppositional defiant disorder was triggered and worsened by his familial context (his parents were on the verge of splitting up, with frequent quarrels). When last evaluated by us, at age 16 years, height was 160 cm (3rd centile), weight 47 kg (3rd centile), and OFC 52 cm (<2nd centile). Highly arched palate, hypotonic face with drooling, diffuse hypotonia, joint hyperextensibility, and low frontal hairline were noted. He still showed some degree of hyperactivity, with an inconstant oppositional defiant behavior. When thwarted, he tended to react with aggressiveness. However, over time, he has shown a slow, but global evolution of the adaptive behavior, and social interaction, with an improvement in the communicative skills (mainly directed at his own needs) and verbal comprehension. At present, he is able to help with simple household tasks, such as setting and clearing the dinner table, cleaning up dust, putting dirty clothes in hampers, putting in order his own toys; shutting windows and doors, and throwing away trash. His rehabilitation plan includes a specific program to improve his social interaction, and his tolerance to frustrations.

Patient 3

Patient 3 is a 13½-year-old boy with idic(15) syndrome who was born in 1997. Firstly, we had seen him at age 9 months for developmental delay. He was the forth child of healthy nonconsanguineous parents, born at term, by normal delivery, after an uneventful pregnancy. Family history was noncontributory. On day 2 of life, following a cyanotic episode, he was diagnosed with VSD and TGA, surgically treated. He was artificially fed with a reportedly good suction. Psychomotor delay was obvious early. He held his head at 8 months, sat with no support at 14 months, and walked independently at 2½ years. He never developed expressive language, and comprehension was very limited and contextual. He was withdrawn from early on, showing no interest toward his peers, being very passive, with no eye-to-eye contact. Several gestural, head and mouth stereotypies were seen. Bouts of inappropriate laughter could be seen from time to time. He first smiled at his mother at around 8 months of age. He never achieved sphincter control. He used to call for discomfort by crying. When firstly evaluated by us, at age 9 months, he had bilateral epicanthal folds, broad, flat nasal bridge, diffuse hypotonia with lax ligaments. He had his first seizure at age 6 months, followed by several other episodes, treated, elsewhere, with a variety of drugs (Phenobarbital, Lamotrigine, Carbamazepine, Phenytoin, Clobazam). When last seen by us, at age 6 years, he had a severe/profound ID (IQ 20) with no speech. He had a nonfunctional use of the objects, which were explored through sensorimotor patterns (liking and/or smelling them). Gesture repertoire was very poor. When requested to do something, he used to respond with the prosthetic use of the adult, not associated with eye contact. He had a poor eye-to-eye contact, with a reduced mimic expressivity. There were no behaviors such as showing or drawing attention of the other to share attention, pleasure, or enjoyment. No imitative play was ever observed. Height was 120 cm (75th–90th centile), weight 23 kg (75th–90th centile), and OFC 52 cm (50th centile). Mildly low-set, posteriorly rotated ears, deep-set eyes, mild bilateral epicanthal folds, hypotonic face with drooling, diffuse marked hypotonia, and joint hyperextensibility were noted. He showed an aimless hyperactivity, with oppositional-defiant behavior. When thwarted, he reacted with aggressiveness. The VABS [Sparrow et al., 1984] showed a total age equivalent of 15 months. ADOS-G Module 1 (Pre-Verbal/Single Words) [Lord et al., 2002] gave the following scores: Social Interaction Total 12 (autism cut-off = 7); Communication

Total 7 (autism cut-off = 4); Total score 19 (autism cut off = 12) consistent with a diagnosis of autism. Besides, the third area (stereotyped behaviors and restricted interests) score was 3.

ADI-R [Lord et al., 1994] gave the following scores: qualitative compromission of social interaction 27 (cut-off = 10), communication 14 (cut-off = 7), repetitive behaviors, and stereotyped patterns 4 (cut-off = 3), consistent with a diagnosis of autism.

Until age 10 years he has shown a slow, but global evolution of the adaptive behavior, and social interaction, with an improvement in the communicative skills (mainly directed at his own needs) and verbal comprehension, and some decreased occurrence of withdrawal behavior. Since then, there has reportedly been a sort of stop in his slow improvement.

At last evaluation, at age 13½ years, he still did not have any sphincter control; was passive, did not help with simple household tasks, and overtly avoided eye-to-eye contact. He was described by his parents as being very "nervous," at times hitting his head and lower limbs with his fists, and, when, stopped by mother, hits the furniture or the house walls. Thereafter, he lays quite for a while. Presently, he attends a rehabilitation center, being enrolled in a personalized rehabilitation plan that includes a specific program to improve his social interaction, and his tolerance to frustrations.

Patient 4

Patient 4 is a 12-year 4-month-old girl with idic(15) syndrome who was born in 1998. Firstly, we had seen her at age 10 years 8 months for evaluation of daily epileptic seizures. She was the second child of healthy non-consanguineous parents, born at 36 weeks gestation, by programmed caesarian, after an uneventful pregnancy. Family history was non-contributory. Her prenatal and immediately postnatal periods were unremarkable. She was artificially fed, with poor suction. Diffuse hypotonia and. psychomotor delay were obvious early. She held her head at 6 months, sat with no support at 12 months, walked independently at 2 years, and pronounced her first words at 3 years. She soon appeared quite withdrawn. At 9 years 9 months she had her first seizure, soon followed by several/day fits, not controlled by different antiepileptic drugs. At 10½ years she achieved sphincter control, and at age 11½ she had her menarche.

When firstly evaluated by us, at age 10 years 8 months, she had very frequent and prolonged daily epileptic seizures. Adjustment of her antiepileptic polytherapy resulted in a fairly satisfactory seizure control. Menarche triggered once again weekly seizures, which were eventually controlled by a subsequent drug adjustment (valproic acid, lamotrigine, rufinamide). At follow up, at age 11 years 8 months, she had a mild-to-moderate ID (IQ 52), and was able to pronounce full sentences. On occasions, there were a few repetitive sentences, and rare gestural stereotypies. The gesture repertoire appeared good. Comprehension was adequate to the context. She was still hypotonic, with some drooling, and joint hyperextensibility. Height was 152 cm (75th centile), weight 42 kg (50th–75th centile), and OFC 53.5 cm (60th centile). Mildly deep-set eyes, bilateral epicanthal folds, hypotonic face with drooling, diffuse marked hypotonia, and joint hyperextensibility were noted. ADOS-G Module 2 (Phrase Speech) [Lord et al., 2002] gave the following scores: Social Interaction Total 3 (autism cut-off = 6; autism spectrum cut-off = 4); Communication Total 2 (autism cut-off = 5; autism spectrum cut-off: 3); Total score 5 (autism cut off = 12; autism spectrum cut-off = 8) not consistent with a diagnosis of autism or autism spectrum. Besides, the third area (stereotyped behaviors and restricted interests) score was 3.

She was able to share enjoyment and pleasure with the other, utilizing both verbal and non-verbal channels, such as the eye contact and the facial mimic expression. She showed fairly good reciprocal social interactions. An overall improvement was seen over time, with a better attention toward the task, and increase in the programming, monitoring, and self-control conducts. She was just acquiring the main personal self-independence skills, concerning self-hygiene, self-feeding, and self-dressing.

Patient 5

Patient 5 is a 1-year-7-month-old girl with idic(15) syndrome who was born in 2008. Firstly, we had seen her at age 1 year for evaluation of DD and hypotonia. She was born after a first dizygotic twinning pregnancy, following IVF with ovum donation, at 35 weeks gestation, by Cesarian due to fetal distress. Apgar was reportedly 9/10. She was initially fed via a naso-gastric tube with both breast and artificial milk, and then orally, with poor suction. Diffuse hypotonia and psychomotor delay were obvious early. She held her head at 6 months, sat with no support at 18 months, and started babbling at 15 months. She soon appeared withdrawn, with no smile, no eye-to-eye contact, and no interest toward the objects. At 7 months she had her first seizures, as infantile spams, associated with an hypsarrhythmic EEG, treated with ACTH and valproic acid, with a good outcome. Since age 12 months, she has been showing a slow but overall improvement, with the appearance of the intention smile and some developmental progress. At follow up, at age 1 year 7 months, she had a moderate ID (IQ 47), and was babbling, turning herself when called, attentive to the verbal message, and interested to sounds. She was also able to respond, at times, to simple verbal requests, with appropriate actions within routines (i.e., "where is your little finger?"; "clap your hands!"). She was able to show some positive affection; preferred familial people; helped to drink from a cup. The spontaneous actions with the objects were characterized by beating (to obtain sound stimulations), shaking, and, at times, oral exploration. To call for something, she used to hand-clap over the table, and/or to vocalize. She was also able to triangulate her attention (glance directed toward an object—her mother—the psychologist), and showed

brief conducts of sharing the pleasure (eye-to-eye contact and smile toward the other). She was able to imitate simple gestures (hand-clapping), and vocalized tunefully to self and others. Height was 79 cm (10th–50th centile), weight 10.5 kg (10th–50th centile), and OFC 44 cm (<2th centile). Prominence of the metopic suture, broad forehead, mildly deep-set eyes, hypertelorism, down-slanting of the palpebral fissures, broad and flat nasal bridge, hypotonic face with drooling, a sacral dimple, diffuse marked hypotonia, and joint hyperextensibility were noted. The CARS showed a score of 25 (cut-off for autism = 30).

DISCUSSION

There is a consistent behavior phenotype in idic(15) syndrome individuals (Fig. 1). It is important to suspect idic(15) syndrome in any infant, child, or adolescent with early central hypotonia of variable degree, dysmorphic features, developmental delay/ID, hard to control epilepsy, and autism or autistic-like behavior. usually subtle and mainly involving the face; while major malformation are rare [Battaglia et al., 1997; Battaglia, 2005, 2008]. This is the main reason for which chromosome analysis may not thought to be indicated in such patients, probably leaving a number of individuals with no diagnosis.

It is important to suspect idic(15) syndrome in any infant, child, or adolescent with early central hypotonia of variable degree, dysmorphic features, developmental delay/ID, hard to control epilepsy, and autism or autistic-like behavior.

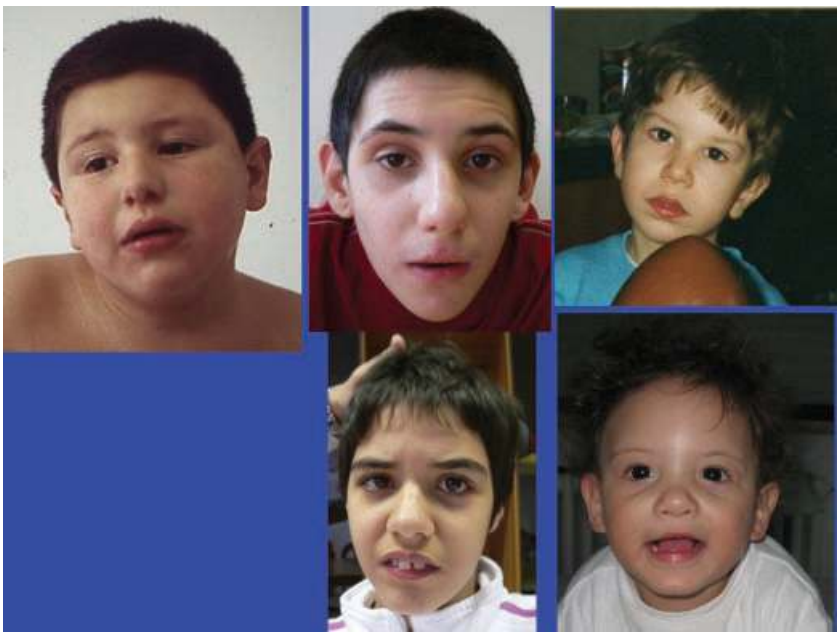

Figure 1. An illustration of the typical behavior in idic(15) syndrome can be particularly appreciated in Patient 1, (top row, left) showing no eye-to-eye contact and passiveness; in Patient 2 (top row, middle) showing defiant behavior; and in Patient 3 (top row, right) staring at people as looking through them. Patient 4 (bottom row, left) was suffering very frequent daily seizures when the photo was shot. Patient 5 (bottom row, right) was showing eye-to-eye contact and smile toward the other.

Idic(15)s have been frequently associated with hyperactivity, aggressiveness, psychomotor agitation, low frustration tolerance, short attention span, ritualistic behavior, stereotypies, and autistic behavior [Wisniewski et al., 1979; Schinzel, 1981, 1990]. The oppositional defiant behavior is usually triggered and worsened by a specific environmental context (within the family; or at school), as clearly observed in our Patient 2. Therefore, stressors in the social, school, and family life should be searched for, in order to control such a behavior. Idic(15) kids show a severe expressive language deficit with the majority only able to pronounce dysillabic sounds or single words; often with immediate or delayed echolalia, and pronoun reversal. These language deficits may lead to secondary behavior problems and difficulties in performing routine daily living skills, such as toilet training, feeding, or dressing. The low tolerance to frustration and the attention problems may also be related to their very poor expressive language skills. Hypotonia, that can be very marked, and joint laxity, which are common in idic(15) syndrome, can cause joint misalignment and pain, contributing to maladaptive behaviors. Nocturnal seizures and certain epilepsy types (i.e., Lennox–Gastaut or Lennox–Gastaut-like syndrome) do disrupt the usual sleep cycle, contributing to stress, low frustration tolerance, emotional lability, and passiveness. Polytherapy for seizures can cause side-effects, leading to additional stressors. Facial hypotonia with drooling is a consistent finding in idic(15) children. Thus, oral motor therapy to improve tone, strength, and coordination would be appropriate.

Interpretation of the association between autism or autistic-like behavior and idic(15) is made difficult by lack of detailed behavioral descriptions and standardized testing for autism in reported patients. However, the association of idic(15) and autism appears to be stronger than that explained by the risk for autism posed simply by coexisting ID and epilepsy. The distinct behavior disorder shown by children and adolescents with idic(15) syndrome has been widely described as autistic

or autistic-like. A strong association between autistic features and isodicentric chromosome 15 [idic (15)] was reported by Rineer et al. [1998], in 20 out of the 29 patients studied. However, these individuals were assessed by telephone interview conducted with a single family member, through the administration of the Gilliam Autism Rating Scale (GARS) [Gilliam, 1995]. The idic(15) patients reported by Borgatti et al. [2001] were said to meet the clinical criteria for the diagnosis of autistic disorder by DSM IV [American Psychiatric Association (APA), 1995]. Assessment of autistic behavior in those individuals was performed with parents' interviews and videotape analysis, through the behavioral summarized evaluation (BSE) scale.

As shown by our patients, most idic(15) individuals meet, in early years, the clinical criteria for the diagnosis of autistic disorder by DSM IV. They have gaze avoidance from very early on; shun body contact; stare at people as looking through them, and can be fascinated by certain sounds, by the water, or by spinning or any glittering objects. Most of them prefer being left alone, lying on the back just looking at their fingers and taking bizarre postures. Symbolic play is usually never acquired. They show no interest toward their peers, and usually do not develop appropriate social interactions. When thwarted they can react with outbursts of shouting or with aggressiveness. Stereotypies are frequently seen, including hand flapping, hand-wringing, hand-clapping over plane surfaces, finger biting, head turning, spinning him/herself for long periods of time. The above behavior, although improving over time, tends to persist in our patients with a severe–profound ID. All our patients with severe–profound ID, but one (described herein as Patient 2), showed ADIR, ADOS-G, CARS scores consistent with a diagnosis of autism. The apparent contradictory ADOS-G (autism spectrum) and ADIR (no autism) scores obtained in our Patient 2, with a severe ID, could be explained by the fact that the ADOS-G assessment was performed when the patient behavior disorder negatively affected the observation. In fact, at follow-up, we could observe a definite overall improvement, mainly concerning communication and socialization. When dealing with individuals with severe–profound ID, we should keep in mind that the degree of cognitive impairment may lead to an overestimate of ASD using standard diagnostic measures in idic(15) patients. Most, simply, do not reach a mental age at which reciprocal social interaction and skills such as pointing and joint attention would be expected to emerge. In fact, ADIR and ADOS-G give reliable results from a diagnostic point of view only if the assessed patient has a chronological age of 4 years and a mental age of 24 months for the ADIR; and at least a mental age of 18 months for the ADOS-G.

When dealing with individuals with severe–profound ID, we should keep in mind that the degree of cognitive impairment may lead to an overestimate of ASD using standard diagnostic measures in idic(15) patients. Most, simply, do not reach a mental age at which reciprocal social interaction and skills such as pointing and joint attention would be expected to emerge.

Of note, two patients (described herein as 4 and 5) out of 13 had mild–moderate ID and did not meet the DSM-IV criteria for autism.

Non-functional use of objects with a primordial type of exploration (sucking, liking, and/or smelling) has been a constant behavioral feature in our idic(15) patients, and was associated with selective and restricted interests (well highlighted in Patients 1 and 3). Such clinical observation has been confirmed by the high score in the third ADOS-G and ADI-R area (concerning play, stereotyped behavior, and restricted interests), in all our patients, both with and without autism. In our clinical experience, similar high scores in the third area are usually not found in "idiopathic" ASD patients.

In conclusion, the degree of cognitive impairment, the evolution of behavior over time, and the high score in the third ADOS-G and ADI-R area, suggest a distinct developmental profile in idic(15) patients, that may provide a behavioral signature for ASD/ASD-like arising from the susceptibility locus on proximal 15q. We propose that idic(15) individuals are not "true autistic," but distinct "autistic-like" persons with high score in the third ADOS-G and ADI-R area.

The degree of cognitive impairment, the evolution of behavior over time, and the high score in the third ADOS-G and ADI-R area, suggest a distinct developmental profile in idic(15) patients, that may provide a behavioral signature for ASD/ASD-like arising from the susceptibility locus on proximal 15q. We propose that idic(15) individuals are not "true autistic," but distinct "autistic-like" persons with high score in the third ADOS-G and ADI-R area.

REFERENCES

American Psychiatric Association (APA). 1995. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association. p. 67–80.

Battaglia A. 2005. The inv dup(15) or idic(15) syndrome: A clinically recognisable neurogenetic disorder. Brain Dev 27:365–369.

Battaglia A. 2008. The inv dup(15) or idic(15) syndrome (Tetrasomy 15q). Orphanet J Rare Dis 3:30. Available at: http://www.ojrd.com/content/3/1/30.

Battaglia A, Gurrieri F, Bertini E, Bellacosa A, Pomponi MG, Paravatou-Petsotas M,

Mazza S, Neri G. 1997. The inv dup(15) syndrome: A clinically recognizable syndrome with altered behaviour, mental retardation and epilepsy. Neurology 48:1081–1086.

Blennow E, Nielsen KB, Telenius H, Carter NP, Kristoffersson U, Holmberg E, Gillberg C, Nordenskjold M. 1995. Fifty probands with extra structurally abnormal chromosomes characterized by fluorescence in situ hybridization. Am J Med Genet 55:85–94.

Borgatti R, Piccinelli P, Passoni D, Dalprà L, Miozzo M, Micheli R, Gagliardi C, Balottin U. 2001. Relationship between clinical and genetic features in "inverted duplicated chromosome 15" patients. Pediatr Neurol 24:111–116.

Browne CE, Dennis NR, Maher E, Long FL, Nicholson JC, Sillibourne J, Barber JC. 1997. Inherited interstitial duplications of proximal 15q: Genotype–phenotype correlations. Am J Hum Genet 61:1342–1352.

Cheng SD, Spinner NB, Zackai EH, Knoll JH. 1994. Cytogenetic and molecular characterization of inverted duplicated chromosomes 15 from 11 patients. Am J Hum Genet 55:753–759.

Christian SL, Fantes JA, Mewborn SK, Huang B, Ledbetter D. 1999. Large genomic duplicons map to sites of instability in the Prader–Willi/Angelman syndrome chromosome region (15q11–q13). Hum Mol Genet 8:1025–1037.

Crolla JA, Harvey JF, Sitch FL, Dennis NR. 1995. Supernumerary marker 15 chromosomes: A clinical, molecular and FISH approach to diagnosis and prognosis. Hum Genet 95:161–170.

Crolla JA, Youings SA, Ennis S, Jacobs PA. 2005. Supernumerary marker chromosomes in man: Parental origin, mosaicism and maternal age revisited. Eur J Hum Genet 13:154–160.

Dennis NR, Veltman MWM, Thompson R, Craig E, Bolton PF, Thomas NS. 2006. Clinical findings in 33 subjects with large supernumerary marker(15) chromosomes and 3 subjects with triplication of 15q11–q13. Am J Med Genet Part A 140A:434–441.

Flejter WL, Bennet-Barker PE, Ghaziuddin M, McDonald M, Sheldon S, Gorski JL. 1996. Cytogenetic and molecular analysis of inv dup(15) chromosomes observed in two patients with autistic disorder and mental retardation. Am J Med Genet 61:182–187.

Gillberg C, Steffenburg S, Wahlstrom J, Gillberg IC, Sjostedt A, Martinsson T, Liedgren S, Eeg-Olofsson O. 1991. Autism associated with marker chromosome. J Am Acad Child Adolesc Psychiatry 30:489–494.

Gilliam J. 1995. The Gilliam Autism Rating Scale. Austin, TX: Pro-Ed. pp. 1–31.

Hou JW, Wang TR. 1998. Unusual features in children with inv dup(15) supernumerary marker: A study of genotype–phenotype correlation in Taiwan. Eur J Pediatr 157:122–127.

Huang B, Crolla JA, Christian SL, Wolf-Ledbetter ME, Macha ME, Papenhausen PN, Ledbetter DH. 1997. Refined molecular characterization of the breakpoints in small inv dup (15) chromosomes. Hum Genet 99:11–17.

Lalande M. 1996. Parental imprinting and human disease. Ann Rev Genet 30:173–195.

Leana-Cox J, Jenkins L, Palmer CG, Plattner R, Sheppard L, Flejter WL, Zackowski J, Tsien F, Schwartz S. 1994. Molecular cytogenetic analysis of inv dup (15) chromosomes, using probes specific for the Prader–Willi/Angelman syndrome region: Clinical implications. Am J Hum Genet 54:748–756.

Loitzsch A, Bartsch O. 2006. Healthy 12-year-old boy with mosaic inv dup(15)(q13). Am J Med Genet Part A 140A:640–643.

Lord C, Rutter M, LeCouter A. 1994. Autism diagnostic review revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.

Lord C, Rutter M, DiLavore PC, Risi S. 2002. Autism Diagnostic Observation Schedule. Los Angeles: Western Psychological Services.

Luke S, Verma RS, Giridharan R, Conte RA, Macera MJ. 1994. Two Prader–Willi/Angelman syndrome loci present in an isodicentric marker chromosome. Am J Med Genet 51:232–233.

Makoff AJ, Flomen RH. 2007. Detailed analysis of 15q11–q14 sequence corrects errors and gaps in the public access sequence to fully reveal large segmental duplications at breakpoints for Prader–Willi, Angelman, and inv dup(15) syndromes. Genome Biol 8:R114.

Maraschio P, Cuocco C, Gimelli G, Zuffardi O, Tiepolo L. 1988. Origin and clinical significance of inv dup (15). In: Danil A, editor. The Cytogenetics of Mammalian Autosomal Rearrangements. New York: Alan R. Liss. pp. 615–634.

Rineer S, Finucane B, Simon EW. 1998. Autistic symptoms among children and young adults with isodicentric chromosome 15. Am J Med Genet 81:428–433.

Roberts SE, Maggouta F, Thomas NS, Jacobs PA, Crolla JA. 2003. Molecular and fluorescence in situ hybridization characterization of the breakpoints in 46 large supernumerary marker 15 chromosomes reveals an unexpected level of complexity. Am J Hum Genet 73:1061–1072.

Robinson WP, Binkert F, Gine R, Vazquez C, Muller W, Rosenkranz W, Schinzel A. 1993. Clinical and molecular analysis of five inv dup (15) patients. Eur J Hum Genet 1: 37–50.

Saitoh S, Hosoki K, Takano K, Tonoki H. 2007. Mosaic paternally derived inv dup(15) may partially rescue the Prader–Willi syndrome phenotype with uniparental disomy. Clin Genet 72:378–380.

Schinzel A. 1981. Particular behavioural symptomatology in patients with rarer autosomal chromosome aberrations. In: Schmid W, Nielsen J, editors. Human Behavior and Genetics. Amsterdam: Elsevier/North Holland. pp. 195–210.

Schinzel A. 1990. Autistic disorder and additional inv dup(15)(pter—q13) chromosome. Am J Med Genet 35:447–448.

Schinzel A, Niedrist D. 2001. Chromosome imbalances associated with epilepsy. Am J Med Genet 106:119–124.

Sparrow SS, Balla DA, Cicchetti DV. 1984. Vineland Adaptive Behavior Scales. Circle Pines, MN: American Guidance Service.

Wang NJ, Liu D, Parokonny AS, Schanen NC. 2004. High-resolution molecular characterization of 15q11–q13 rearrangements by array comparative genomic hybridization (array CGH) with detection of gene dosage. Am J Hum Genet 75:267–281.

Wang NJ, Parokonny AS, Thatcher KN, Driscoll J, Malone BM, Dorrani N, Sigman M, LaSalle JM, Schanen NC. 2008. Multiple forms of atypical rearrangements generating supernumerary derivative chromosome 15. BMC Genet 9:2.

Webb T. 1994. Inv dup (15) supernumerary marker chromosomes. J Med Genet 31: 585–594.

Webb T, Hardy CA, King M, Watkiss E, Mitchell C, Cole T. 1998. A clinical, cytogenetic and molecular study of ten probands with inv dup (15) marker chromosomes. Clin Genet 53:34–43.

Wisniewski L, Hassold T, Heffelfinger J, Higgins JV. 1979. Cytogenetic and clinical studies in five cases of inv dup(15). Hum Genet 50: 259–270.