BEHAVIORAL PHENOTYPES

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Abstract

Complex phenotype in neurogenetic disorders raised scientific interest and implication of novel technologies having the purpose of defining them at different levels: genetic, structural and functional, cognitive and behavioral. This article suggest that that their behavioral phenotype is not a juxtaposition of impaired learning abilities, attention deficit/ hyperactivity disorders or pervasive symptoms and increasing acknowledgement we can design appropriate/ individualized intervention programs for patients, family and community.

Key words: behavioral phenotype, neurogenetic disorders, rare diseeases

Background

Behavioral genetics focuses on human traits and behavior study, analyzing the differences that arise in connection with a trait in the individuals of a population.

The advancement in neuroscience knowledge, the interdisciplinary between biology, epigenetics, ethology statistics, psychology and genetics, have created the path to a better understanding of biological bases of behavior, going towards identifying the neurobiological mechanisms underlying behavioral patterns.

Molecular genetic studies are trying to establish new directions for the mechanisms trough which the human genome fundaments behavioral phenotypes. An argument in this direction is that careful observation of behavior is compulsory when approaching therapeutic interventions in neurogenetic disorders. However, due to reduced incidence of some of these disorders and their complex genetic mechanism, it is difficult to establish the validity of the syndrome-behavioral phenotype association.

A definition considers behavioral phenotype to be a pattern of motor, cognitive, language and social dysfunction characteristics that are associated with a biological disorder. The presence of the behavior is not required in any situation, but the likelihood of its recurrence is increased. [1]

Typical examples are self-mutilation of fingers and lips in Lesh Nyan syndrome (LNS), hyperphagia and compulsive eating behavior in Prader Willi syndrome (PWS), reduced emotional contact in fragile X syndrome (FRX), and superficial sociability, tachylalia, and language disorders in Williams syndrome (WS). When present, the symptoms suggest the syndrome. [2] Using this method, Rett syndrome behavioral phenotype, with stereotypes characteristic of wave motion of the hands, hand-mouth game, made this type of autism identifiable many years before its genetic origin was recognized.

Behavioral phenotypes identification in these disorders was just a step towards a complex work of which can correlate a gene with one or tens of proteins, different genes with the same behavior, more genes and mutations involved more complex the mechanism. [2] However, despite the presentation of behaviors that define the syndrome, not all patients, will present the classic symptoms, but the probability to occur is higher. Behavioral phenotypes also influences acquired disorders, such as, for example in fetal alcohol syndrome. The impact of alcohol on cells is now well known, its consequences are related to cell death, brain median line developmental abnormalities, behavioral problems and learning difficulties.

Why should we be interested in the concept of behavioral genetics? How can it help us?

Firstly, it has clinical value. Identification of these phenotypes may provide clues regarding underlying genetic cause which can explain developmental and behavioral alterations. Increasing awareness of professionals in this field may facilitate access to early diagnosis and development of specific interdisciplinary intervention programs.

The knowledge derived from studies on genetic abnormalities and their behavioral phenotypes in these syndromes are also relevant for studies concerning the biological determinants of human behavior.

For many parents it may be difficult to deal with the illness of their child with unexplained behavior, different from everyone in the family. Parents can be informed that certain behavior patterns are characteristic for their illness (learning disorders or facial dimorphisms) and together they shape their child's specific disease manifestations. Families find empowering the access to full knowledge about their family members' genetic conditional not only by facilitation of the grief process but, more important, helping the coping mechanism, by the access to resources and peer support from other groups with the same condition. Additionally genetic counseling brings further understanding.

This article will detail the patterns of behavior in genetic disorders.

Specific behavioral phenotypes in several rare genetic diseases

A. Lesh-Nyan syndrome (LNS)

Is a X-linked transmitted, recessive disorder with an incidence of 1: 380,000. It involves an inborn error of purine metabolism, due to the absence (or very low levels) of hypoxanthine-guanin phosphoribosyltransferase (HPRT) enzyme. The enzyme deficiency prevents normal hypoxanthin metabolism and produces excess serum accumulation of uric acid, with symptoms of gout in absence of specific treatment.

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Fig.1. 4.5 year old boy with spastic tetraparesis, and sever motor regression because of LNS

Fig.2.Male patient at age of 4. Note the fair skin, clearly nonspecific brown eyes, the hypotonic face with prominent lower jaw, wide mouth, tongue thrusting, and relative microcephaly

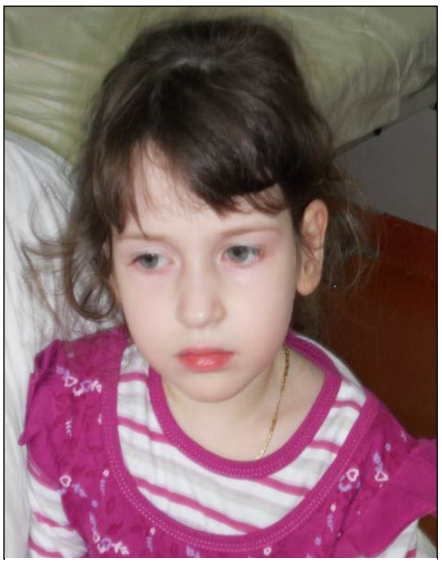

Fig. 3. Our 5 year old patient. Note the lack of contact and interest for the human face.

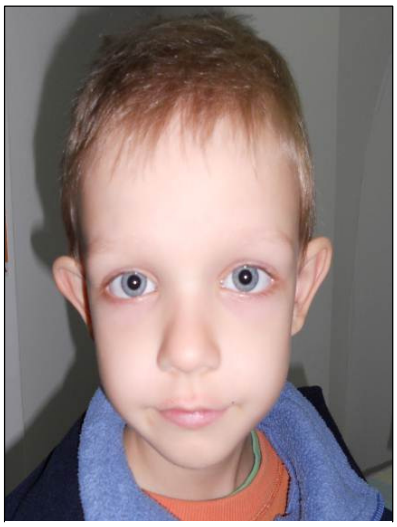

Fig.4. A 5 year old boy with FRX, showing some of the facial features: long face, large and protruding ears, low muscular tone.

Page and Nyan suggested a correlation between the severity of motor symptoms, the presence of self-aggressive behavior, the cognitive assessments and the HPRT level.[3]

Behavioral phenotype

Self-aggressive behavior of LNS was conceptualized as a compulsive behavior that the child tries to control, but which is usually hard to resist. The topography of these can be predicted: the most common, biting of fingers, lips, and oral mucosa, in early years and other maladaptive behaviors (hitting the head, trunk and eyes, nail pulling) or psychogenic vomiting later. Usually these involve mutilating of only one part of the body. Compulsive behavior is preceded by anxiety. These children become anxious when they start to see a part of their body as being threatening. The boys and young men seem to welcome protective restraining devices and appear to become extremely agitated when these are removed.[4] A verbal pattern can be represented by chronic stutter and coprolalia. Moreover, the child may have aggressive impulses and pinch, scratch, or direct verbal insults against other children. [5]Interestingly, some children treated from birth for hyperuricemia, reaching normal levels of uric acid, have developed self-aggressive behaviors.

Case report

We report a 4.5 years male patient. Parents reported "orange sand" in their son's nappies in the first week. He started to manifest severe restlessness episodes, insomnia and difficult acceptance of the bottle around 3 month. Around 6-7 month he started to show developmental delay and motor incoordination. He was diagnosed with LNS around the age of one, already at this age presenting self-injurious behavior like hitting the head and frequent vomiting. They started Allopurinol immediately after the diagnosis. The present developmental status is: cognitive concordant with the age of 36 months. The language is severely impaired; he can use very short sentences of 2-3 words. Motor skills: spastic tetraparesis with uncontrolled extrapyramidal movements. Usually a happy child, he learned to anticipate the self-aggressive outburst and to ask his mother to protect him. Even wearing special gloves, pacifier and helmet he mutilated his lips, teeth and gingival mucosa. The parents report that the medical management included a whole range of medical treatment including SSRIs, antipsychotics, dopamine antagonists, anxiolytics and opiate antagonist, gum shields and some teeth removing.

B. Prader-Willi Syndrome (PWS)

PWS is caused by the loss of paternal copies located in the region 15q11-13 usually by deletion. The maternally inherited copies of these genes are virtually silent due to imprinting in this region, only the paternal copies of the genes being expressed. Other genetic mechanisms include: uniparental disomy (UDP), sporadic mutations, chromosome translocations, and gene deletions. Deletion of the same region on the maternal chromosome causes Angelman syndrome (AS).

Despite its prevalence of 1/10.000 up to 1/15.000 the behavioral phenotype came to be remarked in relation with Angelman syndrome, which has a different behavioral phenotype although both genomic imprinting disorders are involving the same region on chromosome 15. PWS and AS represent the first reported instances of imprinting disorders in humans.

Behavioral phenotype

Specifically, the syndrome includes a particular eating behavior (a compulsive search for food, non-selective non-discriminatory ingestion of large quantities of food and also, stealing food), irritability, reduced tolerance to frustration, stubbornness, anger, pinching skin, associated, in the vast majority of patients with mild mental retardation. Behavioral control problems appear as the child grows, initially in transition from one activity to another, and then, associated with binge eating behavior.

Typically, the behavioral difficulties reach a peak in adolescence or in early adult life. Binge eating is the most severe and debilitating behavior disorder, leading to obesity, diabetes and severe respiratory difficulties. Usually, patients are happy and open to interpersonal networking, participating with interest in behavioral training. They can learn to structure their daily routine activities, rewards, breaks, boundaries and firm rules.

An extensive study focused on assessing self-aggressive, stereotyped and obsessive compulsive behavior in individuals with PWS and showed that skin picking is the most common self-aggressive behavior, observed in 19.6% of individuals, with low frequencies of nose pinching, kicking and pulling nails and lips hair. From the compulsive behavior category, the compulsive eating is the most common. Less common are the rigidity and inflexibility to environmental changes, strict arranging of objects, repeated checks, compulsive washing of hands. [6 7]

Standardized assessments have identified high levels of depressive, anxiety and compulsive symptoms, with functioning impairment, which are not explained by developmental delays, difficulties in nutrition or by obesity in patients with PWS. [8]

Case report

We report a 12 years old male patient diagnosed at age of 2 as having PWS after a history of neonatal hypotonia and difficulties in achieving the important developmental milestones. The parents manage to control his compulsive alimentary behavior by controlling the environment and cognitive behavioral therapy. He is able to follow a complete behavioral program every day, however, when frustrated he has difficulties in avoiding a binge episode. During this episode he still needs one of his parents to help him relax and not transform the frustration of not finding anything in the fridge in a temper tantrum. BMI at the moment is 28.77kg/m2. He controls the pinching skin habit relatively well. The psychological evaluation revealed: mild mental retardation, severe deficit of executive functions, dyslalia, severe attention deficit and anxiety. He finds difficulties in interacting with children of his age and

making friends, "because of his difficulty playing by the rules" and "not having brothers"?his mother reports?. His medical management includes a carefully chosen diet, growth hormone therapy, stimulants for his attention deficits disorder, overnight CPAP supply for his sleep apnea.

C. Angelman Syndrome (AS)

Is a neurological disorder caused by a deletion or inactivation of genes on the maternally inherited chromosome 15 while the paternal copy, which may be of normal sequence, is imprinted and therefore silenced. 20-30% of patients have a biparental heritability and a normal methylation pattern in the region 15q11-q13. In this subgroup the UBE3A gene mutation produces AS.

Behavioral phenotype

The clinical picture comprises of psychomotor development delay, a joyful mood, hyperexcitable personality. Apparent happiness is the brand of the syndrome, associated with a vague smile, rare specific laughs, exuberant background, hyperactive and stereotyped motor behavior, and proactively social contact. Social adaptability is poor, maintained by anxiety and is frequently a source of disappointment for parents who focus on the child's apparent happiness.

Autistic symptoms lead to debates in diagnosis. The absence of expressive language, the reduced and inefficient use of nonverbal communication, motor and sensory stereotypes and sleep problems have all been correlated with low development profile and were considered by some authors as "co-morbid autistic disorder". Peters et al (2004) have found an association between AS and autistic spectrum disorders (according to DSM IV) in approximately one-half of the evaluated cases. [9]

In addition, AS can be associated in various degree with ataxia, epilepsy and microcephaly, all being attributed to the maternal UBE3A allele deficiency. Some children can develop severe myoclonic seizures, knowing that myoclonus with cortical origin is another manifestation of AS.

Case report

We report a 4 years old boy with a history of delayed motor milestones and delay in general development later, absence of speech and poor understanding of language until 1.5 years when he had the first seizure. Soon after the seizure he was seen laughing out loud, hand flapping as the most happy child while having 41 degrees Celsius of fever. The EEG ruled the gelastic phenomenon during this paroxysms of laughter and showed a characteristic pattern with large amplitude slow-spike waves (usually 2–3/s), facilitated by eye closure. Neurological evaluation revealed global severe hypotonia, the child not being able to sit, flat occiput, microcephaly, movement and balance disorder, with ataxia of gait and tremulous movement of limbs, frequent drooling and protruding tongue. The AS diagnosis came as a conclusion of this typical clinical picture and a relief for the parents who had guilt issues of not being able to protect him for a severe cerebral palsy. At the moment he is able to walk, he started to use simplistic sign language. His social interaction is poorly regulated, probably based on his low facial expression decoding. Hyperactivity, low interest exploring pattern and attention, stereotypical flapping of the hands, excessive chewing behaviors are still difficult to control by his therapists. The parents have learned to deal with his episodic severe insomnia, sensitivity to heat, feeding problems and to use his fascination for water as a reward for appropriate behaviour.

D. Rett syndrome (RTT)

RTT is a progressive neurodevelopmental disorder that occurs almost exclusively in females, having an incidence of 1/10.000 to 1/15.000 live births and a penetrance of 100%. [10]. The girls who manifest RTT are usually heterozygous for a de novo mutation in MECP2 gene in 95% of the cases. Other genes have been involved in RS etiology, like CDKL5, FOXG1, NGL1. [11]

Behavioral phenotype

The patients with RTT appear to develop normal until 6-18 month. Some of them achieve appropriate milestones, including the ability to walk and even say a few words. The onset of the developmental regression will be noticed by weight loss, weak muscle posture, progressive microcephaly, scoliosis installation. The neurological deterioration is followed by installation of motor incoordination, ataxia, gait apraxia and seizures. The girls progressively loose the purposeful use of hands and replace it with hand wringing or washing, clapping, flapping and mouthing of the hands movements. Other stereotypical behaviors are the breath abnormalities: hyperventilation, breath-holding, aerophagia, apnea and forced expulsion of air and saliva. These are the most frequently recognized behavior in RTT girls. Other autistic features are unresponsiveness to social cues, loss of eye-to-eye contact, hypersensitivity to sound. After this stage the patients suffer severe physical change: loss of weight and of muscular mass, severe scoliosis which together with breathing abnormalities will cause cardiac abnormalities and generalized dystonia. The behavioral abnormalities include high sensitivity to the external events manifested by anxiety, low mood, teeth grinding, night laughing or crying. [12]

Case report

A 5-year-old girl born of non-consanguineous marriage presented with neuroregression, since 1 1/2 year. She had normal milestones up to 1years, using 4-6 words, being interested in exploring the environment, walking by herself, when the cognitive and motor acquisition apparently stagnated.

At 1 1/2 age she had the first epilepsy seizure presented with status. The medical history revealed evident microcephaly since the age of 3 month. On our examination, she appeared to have a very happy puppet smiley face, hypotonia, ataxia, fine tremor of the upper limbs, feeding difficulties, teeth grinding, inability to stand and walk, absence of eye-to-eye contact, hand wringing and washing movements and autistic behavior. The most severe

stereotypical behavior seems to be the hyperventilation and breath-holding. Her EEG record did not show abnormal interictal modifications in the last year and her social quotient was very low. She lost the ability to use her hands in the first few months after the symptoms starting and the walking in the following 6-8 month. She is very sensitive to external changes, every change in the daily routine increase her anxiety, and aggravates the stereotypical behaviors. She presents constant respiratory alkalosis. Her MRI brain revealed diffuse cerebral atrophy, which was predominantly cortical, suggestive of RTT. She was diagnosed with RTT syndrome in severe regressive phase.

D. Fragile X syndrome (FXS)

Include a broad of disorders caused by the mutation in the fragile X mental retardation 1 gene (FMR1) at Xq 27.3. Full mutation is caused by >200 cytosine-guanine-guanine repeats (CGG) which led to methylation or silencing of the gene and absence of messenger RNA and subsequently of FMR1 protein. The premutation, between 55-200 CGG repeats, is found in carriers and can act like a gain of function mutation. Some boys carriers of the permutation may manifest attention- deficit or/and hyperactivity disorder and autism spectrum disorder (ASD). The expansion from a premutaion to a mutation occurs when FMR1 gene is passed to the next generation. The greater the number of CGG repetition in a female, the greater the risk of expansion to full mutation in the next generation. A carrier mother, having two X chromosomes, has a 50% risk to pass the mutation to the next generation, by having affected/ carrier sons and daughters and also normal children without the FRM1 mutation.[13] When passed by a male, the permutation will only pass to his daughters.The premutaion is more frequent and it can occur 1/250 in women and 1/810 in males.[14] The incidence of the full-mutation allele is lower, around approximately 1/2500. Increasing the level of acknowledgment of the cases having the full mutation and high functioning or having the premutation and neurodevelopmental problems may facilitate the access of these individuals to genetic counseling.

Behavioral phenotype

The behavioral phenotype may be more helpful than physical phenotype in diagnosing the children with FXS because of the absence of the typical physical characteristics in prepubertal period. It has been the subject of extensive studies concerning learning difficulties, mental retardation, autistic features, language impairment, perseveration and attention deficit/ hyperactivity disorder.

The intellectual deficit manifest more severe in males with FRX, in majority with an IQ lowers than 70, than in females, in which the pattern of inactivation of the second X chromosome may improve the outcome. Females having full mutation and normal IQ and may manifest deficits in executive functioning which will relate with their attention and organizational difficulties and instable social relationships. [15]

The behavior of children with FXS include impulsivity, short attention span/ hyperactivity, hyper arousal and sensitivity to auditory, olfactory, and tactile stimulus and relational difficulties symptoms and perseveration, a broad of symptoms from ADHD, autistic and control impulses spectrum. But what of these is, and how is it specific?

The relational pattern is considered to be juxtaposition between friendly social and pervasive developmental disorder in children with FRX. [16] They tend to be more sociable and interested in interaction than autistic people, but their structural anxiety and hyper arousal in new environments may increase the tendency to social avoidance.

Perseveration, a specific behavioral and communicative feature, may be another common field with ASD. This can be seen in speech, by repeating the same word, the same topic, using repeatedly the same inadequate tone just for the need of repetition, without response to the negative insight of the audience. Behavioral perseveration is often recognized and can direct to an evaluation for autism. They may prefer to repeat some activities like spinning objects, stacking toys, but also the same rituals, like eating the same food, washing hands, watching the same cartoons. Motor perseveration can be self-stimulatory like hand flapping, toe walking, spinning or leaping, but also hands biting, excessively chewing of food or of the clothing items.

It has been suggested that there is interdependence between the arousal regulation, attention, and academic performance. [17]An argument in this direction is a different sympathetic and vagal/ parasympathetic modulation pattern observed in these children with FRX by compare with the controls.[18]

The excessive activation of nervous system witch overcome the regulatory mechanism as response to social or environmental stimulation, called hiper arousal, seems to be implicated in relational and language particularities, anxiety and ADHD symptoms in FRX.

The aspect of one of these hiper aroused state can be similar with every human in this state: the behavior is disorganized, with poor attention focus, low capacity of control behavior or language. Children and adults with FRX can describe in this state the felling of somatic/ internal sick/pain, which is often seen as vomiting or abdominal pain in children. The time for them to calm down, is much longer than in other people and it is also dependent of the existence of a free zone. In this situation the language can become sludge, eye contact cannot be established and maintained, they can manifest tantrum, aggression and perseveration.

Usually not showed in firsts meeting of a child with FRX, language and vocabulary may be their strength. An infant may amaze his parents by the spectacular vocabulary acquisitions with low effort. The difficulty intervenes when the kid has to exercise his language in a social environment. The hiper arousal structural pattern, combined with the anxiety triggered by social conversational participation and less self-monitoring and control then its needed together with lifelong experiencing these difficulties build a language which is inadequately perseverative and tangential in FRX individuals.[16]

The triad, over activity, persistent inattention and impulsivity leads to many children with FXS to be also diagnosed with ADHD. Compared with peers with the same developmental level they showed the same degree of motor activity, but significant more inattentiveness, restlessness, distractibility and impulsivity.[18]They show a difficulty to switch visual attention and inhibit repetitive behaviors based on a weakness of executive functions.[16]

Particularities concerning hypersensitivity to stimuli, hiper arousal in social environments triggering anxiety, repetitive behaviors, diminishing attention and contact must be approached therapeutically as early as possible by individualized techniques and environment management.

Case report

We report a boy age 5 years, born from normal pregnancy, with mildly late developmental milestones. Parents observed hand flapping, perseveration and poor eye contact during the first year. They asked for an evaluation for ASD. Single palmar crest, ear cupping and hyper extensive joints directed diagnosis to test for FRX. After FRX diagnosis the child the family started to work with a therapist trained in ASD intervention. She observed particularities difficult to address: inability to establish eye contact, even though he is a very happy and interested of interaction child, high anxiety to minimal changing of the environment, rocking behavior and sucking his sleeves in these stressful situations. The parents chose "to protect" him as much as they could from highly stimulated environments. They observed that after an hiper arousal event usually triggered by social anxiety, like going to park, he was very difficult to calm down and could remain upset for the entire day. His language progressed satisfactory with little help, but the attention could only be maintained for only a few minutes by the age of three. Based on his self-stimulatory behaviors, poor attention and eye contact it has been decided to follow the program of a preschool center for autistic children. Transition period was a lot longer than in autistic children and was described by the parents and the therapist as regressive. Perseveration in language started to be severe, anxiety episodes on daily basis and aggressive episodes frequent. He started vomiting and after complete pediatric checkup anxiety was considered the only cause. Finally, the solution was to work daily with the same therapist, in one to one session, and that him to serve as a security figure in other settings like sport, going to gym or to supermarket. The cognitive evaluation showed borderline mental retardation with good communication score and lower socialization and motor scores. The evaluation with ADOS, a specific instrument for ASD, did not situate him in the autism range.

E. Williams syndrome (WS)

WS is characterized by particular facial appearance, with elfin appearance, cardiac abnormalities/malformations, connective tissue abnormalities, mental retardation or learning disorder, idiopathic infantile hypercalcemia, particular cognitive profile and an unusual personality profile.

The disorder is caused by a deletion of 1.5 megabase the long arm of chromosome 7, including the elastin gene (ELN). The deleted region includes about 25 genes that probably contribute the manifestations of the syndrome, like: LIMK1, GTF2I, GTF2IRD1, CYLN2, STX1A, FZD9, implicated in brain development, visual and spatial orientation, synaptic plasticity, motor coordination.[19 20 21 22 23]

Perhaps the most interesting perspective offered by animal models is the opportunity to develop and test new therapeutic interventions. It was already shown that some of the most serious cardiovascular abnormalities found in ELN (elastin) mice, can be mitigated by introducing a human ELN gene, suggesting that, although not identical, mechanisms causing the disease are somewhat similar in humans and mice. [24] This provides a starting point for pre-clinical testing of pharmaceutical therapies to reduce blood pressure, to decrease smooth muscle cell proliferation and vascular stenosis, which are major causes of mortality in WS. In the future, animal models will probably be just as important for development and testing of new therapies to combat anxiety, disinhibition, visual and spatial deficits, and even mental disability.

Behavioral phenotype

All children with WS have delayed development as follows: 75% have the cognitive and adaptive level corresponding [25 26 27] to their mental retardation, while the remaining 25% have learning disorders. [28 29] Individuals with WS are described by most experts as being extremely sociable, empathic, unable to go unnoticed in the group becoming too close and friendly, showing a very positive social judgment to unfamiliar people.[30 31]. Von Arnim and Engel (1964), were among the first to describe that people with WS show an amazing volubility and a greater ability to establish interpersonal contacts, based on a background of uncertainty and anxiety. [32]

Most adolescents and adults with WS present severe anxiety. Children and adolescents with WS have an increased vulnerability to excessive concern, compared with groups with Down or Cornelia de Lange syndrome and manifest clinical anxiety more than those with PWS. This vulnerability to anxiety contributes to "difficult" temper of people with WS.[33] Although individuals with WS are extremely close, empathetic and sensitive to other people, they have difficulties to make and maintain friends. These difficulties may be due to absence of certain social knowledge explained by the "theory of mind". Thus, social knowledge includes an understanding of the mind as a system of representation (e.g. false faith, irony) and the ability to make rapid social judgments about the mental state of others, based on facial expression and body (e.g. emotional and intentional attributions based on immediate perceptual information). In terms of representation, the child must be able to understand another's mental representation of different and be able to predict behavior based on understanding.

The dissociation of language quality and facial and spatial processing was proposed as a mark of the WS

syndrome. WS phenotype involves a feature of cognitive functions: disturbed spatial processing while processing facial expression is intact. The evaluation of the development level showed small differences between adults and children regarding receptive and expressive language. Tests have documented cognitive profile almost identical to those found in children. Reading, pronunciation, numeracy and social adaptation remains at low levels, along with aging, with functioning appropriate for the age of 6-8 years. In studies on both, children and adults, the peculiarities of intellectual abilities hold up the notion that the syndrome has a particular cognitive, linguistic and functional adaptation patterns. The main difficulties in school adjusting are caused by hyperactivity, lack of concentration and poor attention capacity.[34 35]

Case report

Our patient, an 11 years old girl was diagnosed soon after birth with WS secondary to a severe aortic stenosis and hypercalcemia. At the moment she is a 5th grade student and she is getting extra help at home from a professor to keep her in line with her peers. Global developmental delay was first detected at the age of 6 months. She gained milestones by early education intervention, but she is still has mild mental retardation, scoring better on subtests measuring verbal abilities than on subtests measuring visuo-spatial construction. The school teacher reported that her vocabulary is within the normal range size, the onset of grammatical acquisition begun later and needed more effort from both of them. She is willing to be thought, to learn and to please the teacher and the parents. Her program has to be scheduled in 20 minutes episodes with breaks, for her attention deficit to be kept under control.

The report from school also describes her as joyful, sociable, overly friendly, perceived by the other children to be empathic, but needing adult's reassuring when caring for someone her anxiety increases. Emotional and facial decoding is still challenging for her being a hardener for her structural anxiety. She was also diagnosed with unspecific pervasive disorder because of this poor insight for emotions and low ability to create emotional connections and have appropriate response. Even following therapy the cognitive phenotype in WS may be a maintaining factor for anxiety, obsessional thoughts, and bias thoughts about daily routine decisions and in critical points can be reinforced by psychotrope medication.

Conclusion

Studies on behavioral phenotypes in neurodevelopmental disorders demonstrate complex connections that outline the path from genes to cognition and complex behavioral phenotypes. Behavioral phenotypes arise in mendelian transmitted disorders and non-mendelian inheritance (PWS/AS, FRX). Assessments made in these syndromes show that recognition of the genes involved is only the first step. Identifying the proteins involved and their expression in the brain are critical. In order to clarify their mechanism the use of animal models, the study of neuroanatomy trough brain imaging techniques, and detailed descriptions of behavior are mandatory. In addition, comparative studies between partial variants of the Mendelian disorders (WS), those caused by UPD (PWS, AS) as well as the study of atypical subjects, showing all of the characteristics of the disorder (WS) are the key to understanding developmental pathways.

The delineation of behavioral phenotypes can be a difficult task, but should persuade specialists to persist in identifying gene-behavior relationships and behavioral abnormalities. Delimitation of a behavioral phenotype may be the first step toward molecular characterization of behavior.

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References

1. Harris JC Behavioral phenotypes of neurodevelomental disorders: portals into the developing brain. In Davis, KL Coyle,JT, Charney, D and Nemeroff C. (eds.), Psychopharmacology: the Fifth Generation of Progress, American College of Psychopharmacology, Nashville, TN, 2001.
2. Flint J, Yule W (1994): Behavioural phenotypes. In Rutter MR, Taylor E, Hersov L (eds): ''Child and Adolescent Psychiatry.'' Oxford: Blackwell Scientific, pp 666–687.
3. Nyhan WL. Behavioral phenotypes in organic genetic disease. Presidential address to the Society for Pediatric Research, May 1, 1971. Pediatr Res 1972 Jan;6(1):1-9.
4. Anderson LT, Ernst M. Self-injury in Lesch-Nyhan disease. J Autism Dev Disord 1994 Feb;24(1):67-81.
5. Nyhan WL. Behavioral phenotypes in organic genetic disease. Presidential address to the Society for Pediatric Research, May 1, 1971. Pediatr Res 1972 Jan;6(1):1-9.
6. State MW, Dykens EM, Rosner B, et al. Obsessive-compulsive symptoms in Prader-Willi and "Prader-Willi-Like" patients. J Am Acad Child Adolesc Psychiatry 1999 Mar;38(3):329-34.
7. Bellugi U, Lichtenberger L, Jones W, et al. I. The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weaknesses. J Cogn Neurosci 2000;12 Suppl 1:7-29.

8. Reddy LA, Pfeiffer SI. Behavioral and emotional symptoms of children and adolescents with Prader-Willi Syndrome. J Autism Dev Disord 2007 May;37(5):830-9.
9. Peters SU, Beaudet AL, Madduri N, et al. Autism in Angelman syndrome: implications for autism research. Clin Genet 2004 Dec;66(6):530-6.
10. Bienvenu T, Chelly J. Molecular genetics of Rett syndrome: when DNA methylation goes unrecognized. Nat Rev Genet 2006 Jun;7(6):415-26.
11. Ricciardi S, Ungaro F, Hambrock M, et al. CDKL5 ensures excitatory synapse stability by reinforcing NGL-1-PSD95 interaction in the postsynaptic compartment and is impaired in patient iPSC-derived neurons. Nat Cell Biol 2012 Sep;14(9):911-23.
12. Mount RH, Hastings RP, Reilly S, et al. Behavioural and emotional features in Rett syndrome. Disabil Rehabil 2001 Feb 15;23(3-4):129-38.
13. Conkie-Rosell A, Abrams L, Finucane B, et al. Recommendations from multi-disciplinary focus groups on cascade testing and genetic counseling for fragile X-associated disorders. J Genet Couns 2007 Oct;16(5):593-606.
14. Dombrowski C, Levesque S, Morel ML, et al. Premutation and intermediate-size FMR1 alleles in 10572 males from the general population: loss of an AGG interruption is a late event in the generation of fragile X syndrome alleles. Hum Mol Genet 2002 Feb 15;11(4):371-8.
15. Cornish KM, Li L, Kogan CS, et al. Age-dependent cognitive changes in carriers of the fragile X syndrome. Cortex 2008 Jun;44(6):628-36.
16. Cornish K, Sudhalter V, Turk J. Attention and language in fragile X. Ment Retard Dev Disabil Res Rev 2004;10(1):11-6.
17. Roberts JE, Miranda M, Boccia M, et al. Treatment effects of stimulant medication in young boys with fragile X syndrome. J Neurodev Disord 2011 Sep;3(3):175-84.
18. Roberts JE, Boccia ML, Bailey DB, Jr., et al. Cardiovascular indices of physiological arousal in boys with fragile X syndrome. Dev Psychobiol 2001 Sep;39(2):107-23.
19. Hoogenraad CC, Koekkoek B, Akhmanova A, et al. Targeted mutation of Cyln2 in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. Nat Genet 2002 Sep;32(1):116-27.
20. Hoogenraad CC, Akhmanova A, Galjart N, et al. LIMK1 and CLIP-115: linking cytoskeletal defects to Williams syndrome. Bioessays 2004 Feb;26(2):141-50.
21. Frangiskakis JM, Ewart AK, Morris CA, et al. LIM-kinase1 hemizygosity implicated in impaired visuospatial constructive cognition. Cell 1996 Jul 12;86(1):59-69.
22. Hoogenraad CC, Akhmanova A, Galjart N, et al. LIMK1 and CLIP-115: linking cytoskeletal defects to Williams syndrome. Bioessays 2004 Feb;26(2):141-50.
23. Meng Y, Zhang Y, Tregoubov V, et al. Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. Neuron 2002 Jul 3;35(1):121-33.
24. Fisch GS, Hao HK, Bakker C, et al. Learning and memory in the FMR1 knockout mouse. Am J Med Genet 1999 May 28;84(3):277-82.
25. Frangiskakis JM, Ewart AK, Morris CA, et al. LIM-kinase1 hemizygosity implicated in impaired visuospatial constructive cognition. Cell 1996 Jul 12;86(1):59-69.
26. Hoogenraad CC, Akhmanova A, Galjart N, et al. LIMK1 and CLIP-115: linking cytoskeletal defects to Williams syndrome. Bioessays 2004 Feb;26(2):141-50.
27. Meng Y, Zhang Y, Tregoubov V, et al. Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. Neuron 2002 Jul 3;35(1):121-33.
28. Greer MK, Brown FR, III, Pai GS, et al. Cognitive, adaptive, and behavioral characteristics of Williams syndrome. Am J Med Genet 1997 Sep 19;74(5):521-5.
29. Morris CA, Demsey SA, Leonard CO, et al. Natural history of Williams syndrome: physical characteristics. J Pediatr 1988 Aug;113(2):318-26.
30. Udwin O, Yule W. A cognitive and behavioural phenotype in Williams syndrome. J Clin Exp Neuropsychol 1991 Mar;13(2):232-44.
31. Jones W, Bellugi U, Lai Z, et al. II. Hypersociability in Williams Syndrome. J Cogn Neurosci 2000;12 Suppl 1:30-46.
32. Vonarnim G, Engel P. Mental Retardation Related To Hypercalcaemia. Dev Med Child Neurol 1964 Aug;6:366-77.
33. Tomc SA, Williamson NK, Pauli RM. Temperament in Williams syndrome. Am J Med Genet 1990 Jul;36(3):345-52.
34. Udwin O, Yule W. A cognitive and behavioural phenotype in Williams syndrome. J Clin Exp Neuropsychol 1991 Mar;13(2):232-44.
35. Pankau R, Partsch CJ, Neblung A, et al. Head circumference of children with Williams-Beuren syndrome. Am J Med Genet 1994 Sep 1;52(3):285-90.

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