Review Articles

Neurogenetic Syndromes: From Genotype to Behavioral Phenotype

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ABSTRACT

In recent years, the scientific interest regarding genetic syndromes with mental retardation is improved, and "behavioural genetics" is emerging as a distinct discipline. A number of genetic syndromes have been identified as having a distinctive and consistent pattern. Such patterns are useful in four important ways: as a relevant diagnostic clue, as an helpful clinical management and prevention, as a tool to better explain brain-behaviour relationship, and as a guide towards genes that contribute to the biology of specific human behavioural patterns. Although considerable work is needed yet to ensure understanding of the genotype-phenotype relationships, syndromes with mental retardation of known genetic origin will likely play an important role in helping to discover new "cognitive" or "behavioural" genes. Thanks to the improvement of our knowledge, neurobehavioral and psychiatric aspects of specific syndromes have been better delineated. It's evident how neurology paediatricians and clinical geneticists must cooperate in diagnostic clue and follow up, sharing multidisciplinary knowledge. After characterizing of genes involved in specific mental retardation syndromes, we are today in front of one of the more difficult goals: the identification of pathogenetic mechanisms to explain the complexity of clinical and neurobehavioral phenotypes. Only in this way, we shall achieve early and specific diagnoses and, above all, we shall understand the complexity of the disturbs and refer to appropriate medical and social service agencies. **(Int. J. Ch. Neuropsychiatry, 2005, 2(2): 97-101)**

INTRODUCTION

In recent years, advance in molecular biology has transformed the study of mental retardation into a rich area for research and clinical practice. Candidate genes and gene products responsible for mental retardation syndromes has been identified; advance in diagnosis has followed, and geneticists have started recognizing not only physical phenotypes, but also behavioural patterns specific to genetic syndromes.[1]

A behavioural phenotype is defined [2] as a specific and characteristic behaviour repertoire exibited by patients with a genetic or chromosomal disorders. It includes a wide range of developmental and behavioural characteristics including cognitive, motor, linguistic and social aspects as well as behavioural problems and psychopathology [3].

These patterns of behaviour must be consistently associated with the condition inasmuch as a casual relationship is implied between the genetic lesion and the behaviour.

STUDIES OF BEHAVIORAL PHENOTYPES: GOALS

Updated knowledge of behavioral phenotypes is important for every child and adolescent psychiatrist. Some patients will be

referred because of their behavioral problems. The psychiatricist's ability to identify the evident symptoms as a part of a behavioral phenotype will allow an accurate diagnosis and genetic counselling.

It is reassuring for parents to know that some features of behaviour can be a characteristic of the disorder such as facial dismorfism or learning disabilities and so they are neither related to parental skills or their fault.

Besides, the recognition that a syndrome is associated with a distinctive behavioral phenotype can be useful to give information to parents regarding potential future problems. Families can make contact with appropriate resources such as behavioral therapists, or with parent associations. The atypical cognitive and language profile seen in children with specific syndromes has allowed the development of hypothesis regarding brain structure and function. At present the correlation between the identified gene and the pathophysiology of the behavioral phenotype is speculated in only a few syndromes, but every day new genes are discovered and the new advance on molecular mechanisms will increases the number of the syndromes.

GENETIC BASES OF BEHAVIOR: NEUROGENETIC SYNDROMES

The Turner syndrome, which is a genetic disorder that affects 1/2500 females, is characterized by a cohort of clinical findings such as peculiar facies, short stature, gonadal dysgenesis, cardiac and renal abnormalities.

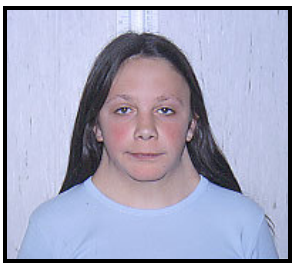

Fig. (1): Turner syndrome.

Turner syndrome is not typically associated with mental retardation. Verbal abilities are generally normal, however, the patients have specific deficits in visuo-spatial abilities, visuo-perceptual abilities, motor function, non verbal memory and attentional abilities. Turner syndrome girls also exhibit impaired executive functions which includes the ability to plan, organize, monitor and execute multistep problem solving processes.[4] They have also hyperactivity, immaturity and low self-esteem. It is important to investigate if abnormalities in cognitive and psychosocial abilities in Turner syndrome girls likely reflect underling aberrant brain development and function in this disorder. With the advent of neuroimaging, structural studies have been used to characterize the neuroanatomical basis of executive and visuo-spatial cognition in this syndrome.

Reiss in 2000 examined a group of 30 girls with Turner syndrome for volumetric differences in brain structures that are known to be linked to executive and spatial impairment.[5]

The study proved that posterior regions and hyppocampus are smaller in the Turner group while temporal lobes and CSF are larger. In another study the relative decreased proportion of the parietal lobe in a Turner girl was demostred Williams syndrome is a contiguous gene deletion disorder caused by haploinsufficiency of genes at 7q 11.23.[6]

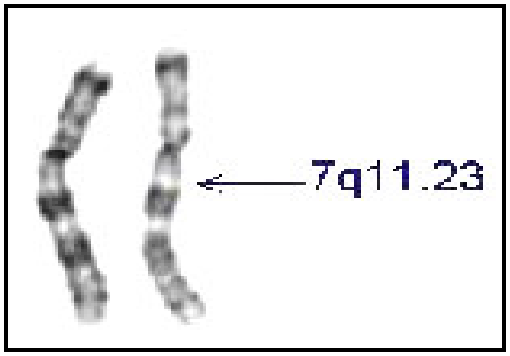

Fig. (2): Williams syndrome.

It is very difficult to make a diagnosis in a newborn; in the first years of life the facial characteristics become evident. They have flat nasal bridge, anteverted nostrils, wide mouth with fleshy lips, periorbital fullness, epicanthic folds. Over time, subcutaneous tissue is lost and can give rise to a prematurely aged appearance. The neurobehaviour is very typical. .Williams syndrome is associated with mild to moderate mental retardation with a mean IQ of 60 and ranging from 40-90.[7]

Individuals with Williams syndrome have a characteristically uneven neurocognitive profile with severe deficits in visual spatial ability but with relative preservation of linguistic competence, particularly in semantics, vocabulary and affective prosody. However the neurobehavioral phenotype associated with Williams syndrome is more complex than a simple visual/verbal contrast.[8] The first gene identified in the critical region was Elastin (ELN) and it has been shown that hemizygosity for elastin causes SVAS and, perhaps, the premature aging of the skin.

Besides, there are many other genes which contribute to the cognitive and behavioral phenotype. The most studied is LIMK1 a protein tyrosine kinase expressed in the developing brain.

It has been suggested that LIMK1 hemizigosity contributes to the visual/spatial deficit.

However the common Williams syndrome deletion region has not been completely characterized and genes for additional features, including mental retardation and the unique personality profile, are yet to be discovered.[7]

VCF syndrome is the most common microdeletion genetic syndrome (1 in 4000 births) caused by the 22q11.2 microdeletion.

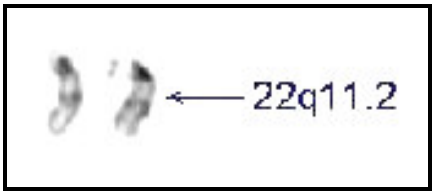

Fig. (3): Velo-Cardio-Facial syndrome.

All patients have learning difficulties. There is also a strong association with psychiatric morbidity. If we analyze the hypothetic relationship between an aspect of the behavioral phenotype and the specific genotype, we can study the attention deficit hyperactivity disorder. The very high prevalence of ADHD found in VCF patients, especially males, suggests that in the 22q11.2 deleted region harbors a gene or genes that contribute to the etiology of ADHD in this population. Interestingly, Quian et coll. recently reported an association between the low-activity of COMT- Met allele located in 22q11.2 region, and ADHD in normal children.[9]

Together, these findings suggest that a reduced dosage of the COMT gene may be a risk factor for ADHD in VCFS children.

The ADHD in subjects with VCF may be the result of a combination of genes located in the 22q11.2 region and other modifier genes located elsewhere in the genome. In our experience children with VCFS tend to be more inattentive than hyperactive and this is confirmed by the literature, while Williams syndrome children seem to be more hyperactive.

Thus, it may be hypothesized that the 22q11 region harbors gene/s (e.g. COMT) mediating attention and the 7q11 region deleted in Williams s., harbors genes regulating activity.

Prader-Willi syndrome is a complex, multisystem mental retardation disorder that has characteristic behavioral phenotype and may include psychiatric abnormalities.

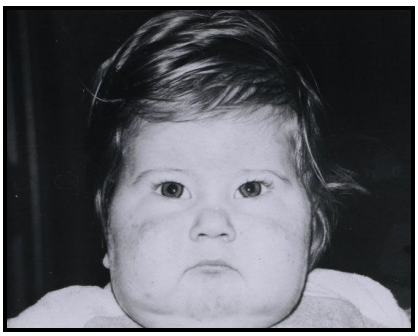

Fig. (4): Prader-Willi syndrome.

It occurs in approximately 1/10000 individuals. It is due to absence of the paternal contribution to 15 (q11-q13), a region affected by a genomic imprinting. This absence can occur by microdeletion in the paternally derived chromosome 15, by maternal uniparental dysomy, or by a defect in the imprinting process for the region.[10]

Although the specific genes causing the abnormalities are yet unknown, many of the manifestations result from functional hypothalamic insufficiency. The main features of PWS are neonatal hypotonia and failure to thrive, developmental delay and mild cognitive impairment, characteristic facial appearance, early childhood onset obesity, hypogonadism with genital hypoplasia and incomplete pubertal development and mild short stature. There is also a characteristic behaviour disorder that usually begins in the first decade of life and becomes worse at and after adolescence. Cognitive delay is the rule in PWS, and most patients are mildly retarded (IQ 60/70).

Academic performance is poor for cognitive ability. Specific patterns of cognitive strength and weakness have emerged, with relative strength in reading, visual-spatial skills and long-term memory; weakness in arithmetic, sequential processing and short term memory. The characteristic behaviour profile becomes evident in early childhood and worsens in adolescence with temper tantrums, stubbornness, controlling and manipulative behaviour, obsessive and compulsive characteristics and difficulty with change in routine. Lyng, stealing and aggressive behaviour are common. Behavioral and psychiatric problems interfere with quality of life in adulthood.[11]

Although the specific genetic culprits have not yet been identified, the genetic lesions appear to led to hypothalamic dysfunction. Animal experiments have show that the parvocellular oxytocin neurones of the hypothalamic paraventricular nucleus (PVN) are crucial for the regulation of food intake. In the rat these neurones project into brainstem nuclei. Small lesions in the rat PVN are responsible of overeating and obesity.

In a study of 5 PWS boys, Swaab in1997 found a large decrease (42%) in the number of oxytocin expressing neurones and the volume was 54% lower.[12] Despite the multiple signs pointing in the direction of the hypothalamus, several studies have identified other brain regions and neuropeptides as possibly being involved in PWS. A study that included MRI and magnetic resonance spectroscopy showed diffuse minor abnormalities in subjects versus controls, including slightly enlarged ventricles, cortical atrophy and a small brainstem. In addition there has been a report of abnormalities of gamma aminobutyric acid (GABA) in PWS subjects. This neurotransmitter has been the subjects of some interest because the loci for GABA receptor subunits are located in the vicinity of 12q11-q13, telomeric to the PWS/AS critical region.

Sex-chromosome aneuploidy, that present cognitive and neurodevelopmental deficits related to the absence or addition of sex-chromosome material, provide a natural model to test the effects of gonadal steroids on the brain.

The number of supernumerary X-chromosomes appears to be directly related to the incidence of mental retardation. Poor language development is well documented in patients with excess X-chromosomes. In Klinefelter's syndrome (47,XXY cariotype) speech and language development are often delayed, school performance tends to be below grade level and there are specific reductions in verbal IQ scores, short term memory and data retrieval ability, with high incidents of reading disabilities and dyslexia, leading to the speculation that a left-hemisphere dysfunction is involved It has been hypothesized that in cases of supernumerary X, slow rate of prenatal neuronal growth selectively delay the development of the left hemisphere, disturbing the normal process of hemispheric lateralization, specifically the specialization for language functioning.[13]

Human studies suggest a role for endogenous testosterone in determining spatial abilities and

functional lateralization in children and adults. Other case studies do suggest that androgen treatment can enhance endurance and drive, improve concentration and learning ability, and contribute to increased self-esteem and better interpersonal relations in most 47,XXY adults.[14] We previously described a 49,XXXXY case with severe language impairment (verbal IQ: 45, non verbal IQ: 57) and significant behaviour problems as extreme sensitiveness, severe shyness, introversion and low frustration tolerance. The patient, after 1 year of testosterone therapy, reported improvement of mood, increased self-esteem, and better relationship with peers.[15]

Conclusion

Although many questions still remain open, we are heartened by the future prospects of behavioural work in genetic mental retardation syndromes. Specialists across a wide variety of social and biomedical sciences now perform sophisticated, etiology-based studies on different genetic syndromes. The correlations between the identified genes and the pathophysiology of the cognitive and behavioural features in specific syndromes are improving and this is useful to reach a better comprehension of the relationship between brain, gene and behaviour.

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