

Contiguous Gene Syndrome. A Case Report

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Abstract

High-resolution genetic tests, such as microarray-based comparative genomic hybridization, are helping clinicians in the diagnostic “odyssey” of neurodevelopmental disorders. They have particularly been leading to the description of a new kind of syndromes, globally classified as contiguous gene syndromes. Its definition is based on chromosomal abnormalities, either deletions or duplications involving contiguous genes, and there is a wide range in severity and complexity of the associated phenotype. We describe the clinical case of a 15-year-old boy with ichthyosis, obesity, and intellectual disability. A genetic disorder was suspected for several years, and a contiguous gene syndrome was finally established, explaining his phenotype. By reporting this case, the authors emphasize the fact that cases of unexplained intellectual disabilities should be periodically reevaluated, and new diagnostic tools, such as microarray-based comparative genomic hybridization, may ultimately establish the diagnosis.

Keywords: Adolescent; Chromosome Disorders/genetics; Gene Deletion; Gene Duplication; Ichthyosis, X-Linked/genetics; Intellectual Disability/genetics; Syndrome

Introduction

During the 14th century, William of Occam proclaimed the Occam’s razor (law of parsimony): a clinician would like to be able to come up with a unifying diagnosis that would explain all of the patient’s problems. Later, in the 20th century, John Hickam declared that a man can have as many diseases as he damn well pleases, establishing the Hickam’s *dictum*.¹ In our everyday practice, we tend to follow the law of parsimony, but we should keep in mind that not all patients and not all the symptoms will fit this theory. Although we generally like to invoke Occam’s razor, for some patients we cannot follow the rule of diagnostic parsimony.²

The availability of newer and high-resolution genetic tests such as microarray-based comparative genomic hybridization (aCGH) has been helping clinicians solve the diagnostic odyssey of various neurodevelopmental disorders. Microarray-based comparative genomic hybridization testing allows genome-wide screening for copy number variations, thus rapidly enabling the detection of submicroscopic chromosomal deletions and duplications at an unprecedented level. This technique uses two genomes, a test, and a control, which are differentially labeled and competitively hybridized to metaphase chromosomes. The fluorescent signal intensity of the labeled test deoxyribonucleic acid (DNA) relative to that of the reference DNA can then be linearly plotted across each chromosome, allowing the identification of copy number changes. One of its advantages, compared to other developed genetic tests, is that aCGH can be used to quickly scan an entire genome for imbalance, simultaneously detecting aneuploidies, deletions, duplications, and/or amplifications of any locus represented on an array.³ Microarray-based comparative genomic hybridization testing is currently the first-tier genetic test in clinical practice for patients with multiple congenital anomalies, unexplained intellectual disability, or autism spectrum disorders.

The increasing use of aCGH in clinical cases of intellectual disability is leading to the description of new contiguous gene syndromes. These emerge from chromosomal abnormalities, either deletions or duplications in contiguous genes, leading to a wide range of signs and symptoms due to the various affected genes, ultimately resulting in a specific and complex phenotype. They are usually sporadic but occasionally can be familial. Some are well known due to their recognizable pattern of malformations, such as Prader-Willi syndrome and DiGeorge syndrome, but new contiguous gene syndromes are still being identified and reported.^{4,5}

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Case Report

We report the case of a 15-year-old boy who was the third child of a non-consanguineous, healthy couple. His general practitioner referred him for a neurodevelopmental evaluation at the age of 4 due to a suspected language disorder. His past medical history revealed ichthyosis, which was diagnosed in his first year of life as well as obesity with a body mass index over the percentile 99 since he was 5 years old. Concerning his family history, both his teenage brothers had learning disabilities and his maternal grandfather suffered from obesity and had ichthyosis. Regarding his developmental milestones, his mother could recall that he walked autonomously by 15 months and that his first intentional words were only accomplished at 30 months. He started kindergarten at 36 months. By 4 years old, he was referred for a full neurodevelopmental evaluation, establishing the diagnosis of a language disorder and a speech sound disorder. He started weekly speech therapy sessions, albeit with a very slow improvement in his expressive and receptive language skills. Social skills, empathy, and role-playing were always age appropriate. At 5 years old, a diagnosis of global developmental delay was established after scoring 78 in the Ruth-Griffiths developmental scale, and he was referred for occupational therapy and for special education services. By then, his physician referred him for a full etiological investigation, including a karyotype, specific genetic tests for Prader-Willi (deletion of 15q11-q13) and fragile-X mental retardation syndrome - expansion of the cysteine-guanine-guanine (CGG) triplet repeat within the fragile-X mental retardation one gene (*FMR1*) located on the X chromosome - together with a full biochemical panel that included thyroid function values. All the results were normal.

By the age of 6, he started primary school requiring a lot of support from special education services. He showed serious difficulties in learning to read and write as well as understanding elementary arithmetical operations, struggling with simple reasoning.

At 7 years old, a diagnosis of mild intellectual disability disorder was established, scoring 68 in the Wechsler Intelligence Scale for Children, revision III (WISC-III). Being unable to keep up with his peers learning skills, he soon became victim to bullying. This fact, combined with his dermatological problem and obesity, led to self-esteem issues and the requirement for psychological intervention.

By the time he was 10 years old, a full physical examination showed exponential weight increase, with a body mass index over percentile 99, worsening of ichthyosis, flat

feet, dental malocclusion, and brachydactyly (Figs. 1, 2, and 3). By that time, he still had trouble expressing himself clearly, sometimes answering questions with strange utterances. On follow-up by 11 years old, a general evaluation of his learning progression was carried out, revealing a complete inability to either read or write in addition to an average intelligence of 48 on the WISC-III and a percentile score of 2 on the colored progressive Raven matrices. Brain magnetic resonance imaging was normal. Due to his rapidly progressive cognitive deterioration, he was promptly integrated into an alternative and individualized curriculum. By this time, aCGH genetic testing was performed, demonstrating a deletion on Xp22.3 (1.6 Mb), between 6.49 and 8.13 that included various genes, like *STS*, *VCX*, *VCX3A*, *HDHD1*, *PNPLA4*, and *MIR651*.

Due to this result, his mother and siblings were tested for the deletion. Merely the mother aCGH genetic testing revealed the same deletion. The maternal grandfather was unavailable for the study.

Discussion

X-linked ichthyosis is an X-linked recessive skin disorder. It has an incidence of 1:2,000-6,000 in males. Clinically, it is characterized by the desquamation of large,



Figure 1. Photo of the 15-year-old boy showing his large abdomen and gynecomastia consistent with his obesity as well as ichthyosis.



Figure 2. Photo of the 15-year-old boy's lower limbs with ichthyosis.



Figure 3. Photo of the 15-year-old boy's hand illustrating the brachydactyly.

irregular, dark scales on the limbs and trunk. This genetic disorder is caused by a deficit in the steroid sulfatase enzyme, encoded by *STS*, and is often associated with microdeletion at Xp22.3.⁶

The Xp22.3 deletion in males may be associated with intellectual and developmental disabilities, Kallmann syndrome (*KAL1*, Kallmann syndrome 1 protein), and short stature (*SHOX*, short stature homeobox).⁷ The clinical features of the affected genes are related to the deletion size and the resulting phenotype is defined as a contiguous gene syndrome.⁵

Despite being a rare phenomenon, other cases of contiguous gene syndromes have been reported in the literature. In fact, a case of X-linked Kallmann syndrome and ichthyosis due to a single deletion was reported recently. Several genes have been implicated in Kallmann syndrome, including *KAL1*, located in the Xp22.3. This is the same region where the *STS* gene is located. A deletion of this site, involving both *KAL1* and *STS*, causes a contiguous gene syndrome characterized by features related to Kallmann syndrome (hypogonadotropic hypogonadism, metabolic syndrome, anosmia, among others) in addition to ichthyosis.⁸

Likewise, a unique case of contiguous gene syndromes, where aCGH revealed a 1.58 Mb deletion on chromosome 12q13.12q13.13, linking hereditary hemorrhagic telangiectasia phenotype (loss of one *ACVRL1* allele) and intellectual and developmental disabilities (deletion of the *SCN8A* gene), has also been recently reported.⁹

By reporting this case, the authors emphasize the fact that cases of severe or progressing intellectual disabilities might be due to contiguous gene syndromes. Other symptoms, especially if the family history is positive, should raise the suspicion of an X-linked intellectual and developmental disability, and genetic testing should be considered for these children. Studies show that chromosomal imbalance contributes to about 29% of all intellectual and developmental disabilities. As molecular karyotyping would miss only 0.6% of cases with probably disease-causing balanced de novo aberrations, aCGH testing in a patient with intellectual disability would have the highest diagnostic yield (28.9%).¹⁰ Other studies confirmed the strength of high-resolution genomic arrays in diagnosing cases of unknown genetic etiology and suggested that contiguous genomic alterations are the underlying pathogenic cause of a significant number of cases of intellectual and developmental disabilities.^{3,11}

However, in clinical practice, performing aCGH genetic testing in every patient diagnosed with intellectual and developmental disability is not cost-effective and the family reproductive expectation should also be taken into consideration. Therefore, the authors believe that aCGH should be the first-tier genetic testing for unexplained intellectual and developmental disabilities, particularly if moderate to severe intellectual and developmental disabilities, associated with dysmorphic features or congenital malformations, or a positive family history for intellectual and developmental disabilities.

The law of parsimony as well as Hickam's *dictum* frequently become the basis of our clinical thinking. In fact, we should keep in mind that different symptoms may have different etiologies or, as in this case, the same genetic explanation.

WHAT THIS CASE REPORT ADDS

- When genetic testing is considered by the clinician, a microarray-based comparative genomic hybridization should be the first tier for unexplained intellectual and developmental disabilities.
- Apparently unrelated clinical signs can be part of the same syndrome, which is explained by contiguous gene syndromes.
- The spectrum of manifestations of contiguous gene syndromes is highly dependent on the size of the chromosomal disorder and the extent of the genes affected.
- X-linked ichthyosis is a skin disease that should be suspected when there is a positive family history of male attainment.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Síndrome de Genes Contíguos. Caso Clínico**Resumo:**

Os testes genéticos de alta resolução, como a hibridização genómica comparativa baseada em microarranjos, têm vindo a ajudar os médicos na "odisseia" diagnóstica das perturbações do neurodesenvolvimento. Em particular, têm vindo a liderar a descrição de novas síndromes, globalmente classificadas com síndrome dos genes contíguos. A sua definição baseia-se em anomalias cromossómicas, sejam deleções ou duplicações, envolvem genes contíguos, existindo uma grande variedade na gravidade e complexidade do fenótipo associado. Descreve-se o caso clínico de um adolescente de 15 anos com ictiose, obesidade e défice cognitivo. A suspeita de doença genética havia sido

levantada há vários anos e conseguiu-se provar a existência de uma síndrome de genes contíguos, que explica o seu fenótipo. Ao descrever este caso, os autores chamam a atenção para a necessidade de reavaliar periodicamente casos de défice cognitivo inexplicado, e novas técnicas diagnósticas, como hibridização genómica comparativa baseada em microarranjos, podem permitir estabelecer o diagnóstico.

Palavras-Chave: Adolescente; Deficiência Intelectual/genética; Deleção de Genes; Duplicação Génica; Ictiose Ligada ao Cromossoma X/genética; Síndrome; Transtornos Cromossómicos/genética