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CASE REPORT

10q distal trisomy and 15q monosomy as a rare genetic cause for intellectual disability

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ABSTRACT

Intellectual disability (ID) is a neurodevelopmental disorder with a prevalence of %1-3. Genetic factors contribute strongly to the etiology of ID and it remains unknown in up to 60% of the cases. De novo mutations represents a common genetic cause in sporadic cases of ID. In this paper, we aimed to present two siblings with distinctive phenotypical features and neurodevelopmental disorders with an unbalanced translocation, [46, XX der(15) t(10;15)(q24.3;26.1)mat], resulting in trisomy of the long arm of chromosome 10 and monosomy of the long arm of the chromosome 15. These cases are thought to be associated with distal trisomy 10q and monosomy 15q syndromes, respectively. Both trisomy 10q and monosomy 15q are rare diseases with a distinctive clinical profile described.

Keywords: Developmental delay, genetic syndrome, intellectual disability, translocation

INTRODUCTION

Intellectual disability (ID) is a neurodevelopmental disorder characterized by delayed acquisition of developmental milestones in early childhood, resulting in impairments in social, practical and conceptual domains, with a prevalence of %1-3 (1). Genetic factors contribute strongly to the etiology of neurodevelopmental diseases and, underlying genetic mechanisms are shown to be complex and vary from one individual to another (2-5). Although a significant progress has been made in terms of ID genetics with advancing molecular analysis technology over the past decades, the exact etiology of ID remains unknown in up to 60% of the cases (6). De novo mutations represents a common genetic cause in sporadic cases of ID and even accounts for most of the severe ID cases (7). A detailed molecular analyses and systematic breakpoint mapping of the identified de novo chromosomal arrangement abnormalities may shed further light on our understanding of genomic and molecular architecture of ID (7). In this paper, we aimed to present two siblings with shared cognitive and clinical phenotypic findings with an unbalanced chromosomal translocation, resulting in trisomy of the long arm of chromosome 10 and monosomy of the long arm of the chromosome 15 [46,XX der(15) t(10;15)(q24.3;26.1)mat]. These cases' phenotypical features as well as neurodevelopmental pathologies are thought to be associated with distal trisomy 10q and monosomy 15q syndromes. In the literature, a number of researchers have reported both trisomy 10q and monosomy 15q syndromes and their clinical consequences (8).

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CASE 1

33 months old girl was referred to our clinic by genetic department for developmental evaluation. Her father reported concerns with his daughter's development. She was delivered at term by a spontaneous vaginal delivery without complication and her prenatal history was remarkable for intrauterine growth retardation. With respect to developmental history, she rolled at 20 months, independently sit at 30 months old and cannot crawl yet. She has hypotonia and muscle stiffness, had more difficulty with acquiring gross motor milestones than other developmental domains. Yet, she was also delayed in acquiring language and fine motor and social milestones. She did not speak her first words until 30 months old and has 3 words currently. Her parents don't report any behavioral disturbances since birth. No evidence of neglect or abuse detected. During her clinical assessment, it is observed that she had cooing and bubbling without meaningful words, she was able to sit without support, and she was able to grasp object but cannot pass to the other hand. She was alert to the environmental stimuli and able to respond her name, smile back in interactions with a good eye contact. Dysmorphic features including microcephaly, microphthalmia, a flat face with a spacious forehead, small nose with a depressed nasal bridge and low-set ears were noted in her physical examination. In her medical history, family reported that she had undergone an orthopedic surgery for hip dysplasia at the age of two. Her parents have non-consanguineous marriage and there were no previously identified cases of neurodevelopmental disorders including ID in the enlarged families of both parents. In parents' genetic analyses, a balanced translocation of t(10;15)(q24.3;26.1) was identified in mother. Denver Developmental Screening Test-II (Denver II) applied to the case; personal-social domain was at 10-11 months, fine motor and adaptive domain was at 10-12 months, language domain was at 8-9 months and gross motor domain was at 6,5-8 months age standards. Gross motor delay more dominant than other aspects of development. Upon the clinical examination and her developmental assessment, a diagnosis of global developmental delay was given. No psychiatric comorbidities found during examination. The family was given psychoeducation about the developmental milestones and the diagnosis of ID. The family has been counseled to improve the child's skills and the patient was planned to receive special education designed for ID in a special education intuition.

CASE 2

Case 2, elder sibling of the former patient, was 11 years old girl. She was delivered at term by a spontaneous vaginal delivery without complication and her prenatal history was remarkable for intrauterine growth retardation, as her sibling. She had delay in multiple areas of development including motor and language skills. Her parents reported that they were first concerned with their daughter's development around 12-18 months of age. She exhibited delay with acquiring developmental skills as her sibling. She did not speak her first words until age 3 and started putting words together at age 6 and still cannot put 3 words together. She can socially express herself to her parents by gestures. She was diagnosed as global developmental delay at the age of four. She had been on special education for ID since first diagnosis designed for ID in a special education intuition. In the past she had received physical education for orthopedic problems for 2 years. She started walking at age 10. She started elementary school in inclusive settings at age 8. She is at fourth year of primary education currently. Her academical achievements are significantly behind her peers during primary education. She cannot write or read yet. No psychiatric comorbidity detected in the past and present. No medication has been used in the past, or using currently. During clinical assessments, she rarely expressed herself verbally, using one-word answers and a vocabulary of approximately 20 words. She can point what she wants and shake her head for express herself. She had poor fine motor control. She took the instructions, such as showing the body parts of her toy. Her phenotypic appearance was very similar to those of her sibling. In the mental state examination, it is observed that she was cooperated, oriented, and her thought content was poor. Stanford- Binet psychometric test applied and the IQ score was 38, evaluated as Intellectual Disability-Moderate level. The diagnosis and clinical consequences have been re-evaluated to the family and family's expectations has been discussed. The family has been counseled to improve the child's skills. The patient was planned to continue special education. Follow-up examinations planned.

DISCUSSION

This paper discusses a rare genetic variant in two siblings with similar cognitive and clinical phenotypes. Both siblings were carrying the same unbalanced translocation, yielding the karyotype 46, XX; der(15)

t(10; 15)(q24.3; q26.1)mat. Balanced translocations occur when pieces of two chromosomes break off and switch places, creating an altered but balanced set of chromosomes. Carriers of a balanced translocation may not have any pathologic condition, yet when they pass these altered set of chromosomes to the offspring, yielding extra and/or missing genetic material in certain locations, causing an unbalanced translocation. Unbalanced translocations usually associated with genetic abnormalities. (8,9) In our cases, the children had extra material on chromosome 10q and deleted material on chromosome 15q, resulted from a maternal balanced translocation of chromosomes 10 and 15. In the literature, several phenotypical characteristics including dysmorphic appearance and distinct neurocognitive profiles were associated with distal trisomy of chromosome 10q and with monosomy of 15q (9). Distal trisomy of 10q is commonly result from an unbalanced parental reciprocal translocation with another autosomal chromosome or pericentric inversion. Terminal end of the chromosome is almost always duplicated region with the proximal breakpoints ranging from 10q22.3 to 10q26.3 (9). Regarding our cases, region of proximal breakpoints was detected on q24.2. More than 50 cases of distal trisomy of 10q were identified in the previous literature with the distinctive craniofacial findings (a flat face with a large prominent forehead, small nose with a depressed nasal bridge, highly arched eyebrows, short and narrow palpebral fissures, tele-canthus), and pre and post-natal developmental problems including ID, autism spectrum disorder (ASD) and prenatal growth retardation (9-11). Our cases' phenotypes are compatible with literature. The first case's diagnosis is Global Developmental Delay, which is defined as significant (2 or more standard deviations below the mean) delay in two or more given developmental domains: gross and fine motor; speech and language; cognition; personal and social development or activities of daily living. Second case's developmental history is compatible with global developmental delay, she is currently diagnosed Moderate level ID. Musculoskeletal abnormalities including hypotonia, abnormal laxity of joints and other malformations of extremities may also be seen, along with abnormalities of other systems such as renal, respiratory and cardiac systems (8). Regarding our cases, lacking an involvement of internal organs may be explained by the previous findings suggesting that the phenomenology and the severity of symptoms may show variation among individuals, probably depending on the length of duplicated region (9). Monosomy of the 15q, on the other hand, is a rare chromosomal abnormality associated with pre and post-natal growth defects, developmental delay and similar craniofacial findings as of those seen in our cases including microcephaly, broad nasal bridge and low-set ears (12-14). It is assumed that the loss of one copy of IGF1R gene, the gene encoding for insulin-like growth receptor 1, accounts for the growth retardation seen during both intrauterine period and post-natal development (12,15). In conclusion, trisomy of chromosome 10q and monosomy of chromosome 15q are rare chromosomal rearrangement abnormalities that are associated with distinct phenotypical findings. Co-existence of these two genetic variations may be even rarer and may be associated with a poorer prognosis. Clinicians should consider that patients with ID may also have comorbid genetic syndrome in order to have chance for early diagnosis and necessary interventions. Further exploration of the genomic alterations within these chromosomal regions, along with the identification of genes contributing to the molecular mechanisms of ID may be helpful in terms of predicting the prognosis, as well as developing molecular targets of intervention.

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