

Fate of a Consanguineous Marriage: A Case Report

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Abstract: Consanguineous marriages are the crucial factors for several genetic disorders and dreadful syndromes which are the bases of morbidity and mortality in the human population. The genetic disorders are linked to abnormalities in either p or q arms of specific chromosomes. However, reports in the literature are not firm on specificity of phenotypic response to the precise genomic region. In view of a paucity of literature on the subject and the controversies arising with respect to the discordance in phenotypic response, this particular case was found interesting for a report in the literature. This is about a baby whose mother was married to her cousin (a consanguineous marriage). The parents had a family history of cerebral palsy and mental retardation. Genetic analysis of the baby showed deletion at 5p14 and the father had translocation between chromosome 5p13 and 10p14 while the mother was genetically normal. The baby was born healthy but had several complications, till he died at the age of 5. The different complications that the baby suffered included: delayed motor activity and developmental disabilities, psychological derrangement, mental retardation, frequent convulsions, microcephali, delayed speech and language development, dysmorphic face, low set ears and hyper reactivity. There was gross discordance in the specific genome region and the phenotypic observations which appears to be due to the interaction between different loci at 5p in addition to epigenetic influence.

Key words: Consanguineous marriage, baby, fatal genetic disorders, locus, 5p14

INTRODUCTION

The word consanguineous comes from the two Latin words Con meaning shared and Sanguis meaning blood. Consanguinity describes a relation between two people who share an ancestor or share blood. The highest consanguineous marriages reported in North Africa and Asia are usually associated with low socio economic status, illiteracy and rural residence (Bittles, 2001). These marriages are the crucial factors for several genetic disorders and dreadful syndromes which are the bases of morbidity and mortality in human population (Magnus *et al.*, 1985; Bindu *et al.*, 2006; Nalini *et al.*, 2008). The genetic disorders are linked to abnormalities of chromosomes in either p or q arms.

This particular case is relevant to chromosome 5 which is one of the largest human chromosomes and

contains numerous intra chromosomal duplications and deletions yet it has one of the lowest gene densities. These abnormalities are described as evolutionary events and are considered to have a role of mechanism in some physiological variations in addition to reason for some serious genetic disorders (Schmutz *et al.*, 2004). The genomic region p of chromosome 5 (5p) is classified on the basis of the combination of the clinical data and high-resolution banding analysis (Dan *et al.*, 1998).

The chromosome 5 (5p) is the house of several genetic syndromes, including, the Cri Du Chat (CDC) and Autism or the Autism Spectrum Disorders (ASDs). The CDC syndrome is a genetic disorder caused by the deletion of variable size occurring on p of chromosome 5 (5p). The major symptoms of this syndrome are high pitch monochromatic cry (probably linked to an abnormality of the larynx and epiglottis), facial dysmorphism,

microcephaly, neurological disorders and mental retardation. The different clinical symptoms of CDC related with genomic region of 5p are a part of 5p13 and 5p14 is related to moderate to severe mental retardation and microcephaly, remaining part of 5p14 is not linked with any symptoms, 5p15.1 is associated with mild mental retardation, 5p15.2 is related to childhood and adult facial dysmorphism and severe mental retardation, major part of the terminal 15p15.3 causes the speech delay and smaller lower part is linked with the loud monochromatic cry (Mainardi, 2006). In a study on clinical and molecular characterization of 80 patients with 5p deletion, Mainardi *et al.* (2001) found that majority of deletions are associated with CDC syndrome and the patients show great phenotypic and cytogenetic variability. Medina *et al.* (2000) asserted the genomic region to be 5p15.2, a segmental aneusomy syndrome of 5p that is associated with phenotypic characters that include an unusually high-pitched cry at birth, facial dysmorphology, poor growth and severe mental retardation. There appears to be a high degree of variation in clinical presentations with CDC syndrome which might be related to the variation in size and locations of deletions in chromosome 5p (Fang *et al.*, 2008). While 5p14 is not silent in CDC syndrome, Autism and Autism Spectrum Disorders (ASDs) (Pourcain *et al.*, 2010), there are some interstitial deletions (p14.1 and 14.3) which have no association with the phenotypic abnormalities. Furthermore, in a three-generation family, the deletion, 5p14 was not associated with any phenotypic anomalies. This scenario was hypothesized to be either coincidental or must have represented unmasking of an autosomal recessive peroxisomal disorder in the deleted region (Hand *et al.*, 2000).

Autism and/or ASDs represent childhood neuro-developmental and neuropsychiatry disorders which are characterized by insufficiency of verbal communication, impairment of social interaction, language development and restricted and repetitive patterns of interests and stereotypic behaviors. Pourcain *et al.* (2010) reported an association between a high-risk autism locus on 5p14 and social communication spectrum phenotypes in the general population moreover, a genetic variant on 5p14.1 was identified to associate with risk for ASDs. Wang *et al.* (2009) in their extensive investigation (10,000 subjects) on common genetic variants of 5p14.1, associated with ASDs, identified common genetic variants that are associated with susceptibility to ASDs. Strathearn (2009) observed etiology of autism to be both genetic as well as epigenetic. The researcher is of the opinion that autism can explain how the social environment can influence gene expression and social development.

Currently, studies on association of diseases with genes are routinely conducted on a genome wide scale. In this pursuit not only the marginal associations of individual markers with the disease are detected but also the gene-gene and gene-environment interactions (that confer susceptibility to the risk of disease) are identified (Zhang *et al.*, 2011). It is of paramount importance to note that interactions between the genes on a particular arm of a certain chromosome may change gene expression such that the identity of the specific syndrome is not explicit. Hence, many interesting cases of human syndromes are required to be discussed in the literature as and when noticed. The present study is the case of a baby (with a deletion at genomic region 5p14) who had phenotypic similarities with more than one syndrome.

CASE REPORT

The consanguineous marriage and the family history:

She was married to her cousin (a consanguineous marriage). Brother and sister of the man and one of the cousins of the woman had cerebral palsy and were mentally retarded. As an educated family, the couple was conscious of some unforeseen problems and hence, the conception was delayed. However, the couple couldn't withstand the fight against destiny and she conceived during the 2nd year.

Pregnancy and the outcome: Routine check and ultrasound (7th and 28th weeks) were normal. However, 32 weeks, onward, she suffered from nausea and vomiting and also developed chicken pox. She was admitted in hospital at 40+4 weeks as primigravida. The preliminary reports showed; BP (150/140), edema in legs (3+) and reduced fetal movements. At even 40.4 weeks, there were no pains and she failed to progress despite augmentation. Cardiotocograph was non-reassuring and hence an emergency cesarean section was performed and the baby (a male) was delivered (January, 2007) with muconeum aspiration and a loud and abnormal first cry. Baby's weight was 3.2 kg.

First 3 years of the baby: The baby was visibly normal but suffered problems in feeding by breast during the 1st month. Consequently, during the first 1 year, the head control was developed however, the baby wasn't able to turn and lagged behind in creeping, even during 2nd year. The symptoms of cerebral palsy and microcephaly were apparent. Although, born with an abnormal loud cry, he appeared to be dumb during the first 2 years. During the 3rd year, the baby showed symptoms of an abnormal larynx as he used to make loud noises. He was made to

stand with support for few moments. He developed excessive fear to flash of light. At this point he was referred to center for developmental neurology.

Reports from center for developmental neurology: The neurologist at the center for developmental neurology, identified a number of symptoms including delayed motor activity, psychological fears from exposure to light, behavioral symptoms including isolation, lack of social smile, gaze fixing, disturbed sleep, lack of recognition of faces. The baby had seizures and abnormal ECG findings. The baby was put on valporin therapy. During the 4th year the symptoms slightly improved and there was little recognition of mother's face.

While most of the medical problems were treated as they arise, the baby was found to respond well to valporin treatment, he picked up pointing behavior and was able to follow some instructions however, he was only 12 kg, a weight that was disproportionate to his age (4 years). Consequently, the baby was referred to a rehabilitation center where he was subjected to a thorough examination and a detailed report from the center suggested the following medical problems: developmental disabilities, hyper reactivity, mental retardation, frequent convulsions, large head, delayed speech and language development, convulsions, dysmorphic low set ears and use to make meaningless high pitch shouts and noises. The rehabilitation center asked the parents to get the biochemical analysis for plasma amino acids, done for the baby and a genetic analysis done on father, mother and the baby.

Results of biochemical analysis: All the amino acids were in the normal range except cystine and valine which were high and low, respectively as compared to the reference range.

Results of genetic analysis

Mother's chromosomal analysis: The cytogenetic analysis revealed all the metaphases to be normal.

Father's chromosomal analysis: The cytogenetic analysis showed translocation between chromosome 5p13 and 10p14. This finding was consistent in all the metaphases. Such chromosome complement is known to lead to formation of an abnormal gamete and likely to inherit.

Son's chromosomal analysis: The cytogenetic analysis revealed deletion in p14 terminal segment (5p minus) in chromosome 5. This finding was consistent in all the metaphases analyzed. The baby was destined to live for 5 years and his ultimate end came with fatal febrile seizures.

DISCUSSION

The pregnancy and the outcome observed is related to the health of the mother during the third trimester. The episode of varicella-zoster virus infection (chicken pox) during 32 weeks indicted some complications of the pregnancy, like elevated BP, edema in legs, reduced fetal movements, failure to progress despite augmentation and non-assuring cardio tocograph. A recent report in the literature suggest varicella-zoster virus infection in pregnancy to cause serious fetomaternal morbidity and sometimes mortality too (Lamont *et al.*, 2011). The following symptoms were apparent in the baby; cerebral palsy, microcephaly, delayed motor activity, developmental disabilities, frequent convulsions, delayed speech and language development, hyper reactivity, dysmorphic low set ears, high pitch noises and mentally retarded.

The chromosome 5 in this case is shown to have a deletion at p14 which appeared to be an unbalanced translocation inherited from father. The baby had cerebral palsy, a neurological disorder that interferes with motor function and posture. The term cerebral palsy is considered to be brain injury. There are multiple lines of evidence including genetic influences on the occurrence of cerebral palsy (Schaefer, 2008). The cerebral palsy in the baby appears to be of genetic origin. Analysis of genetic history of the family revealed that both maternal and paternal family members of the baby had cerebral palsy.

Nevertheless, a possibility of cerebral palsy being congenital cannot be ruled out as the mother suffered with varicella-zoster virus infection during 32 weeks of pregnancy. The infection with chicken pox in pregnancy is known to cause serious fetomaternal morbidity (Lamont *et al.*, 2011). Most of the clinical findings in the baby are related with neurological disorders which account for the observed behavioral symptoms (isolation, lack of social smile, gaze fixing, disturbed sleep, lack of recognition of faces and high pitch noises). All these symptoms are related to genome region 5p and are common to the loci 13, 14 and 15 of CDC. However, there was no cat cry observed. On the other hand, the baby use to make high pitch noises like that made by people with Tourette syndrome (Bernabei *et al.*, 2010) while there was no genetic concordance.

The delayed motor activity caused developmental disabilities which incapacitated him to achieve head control, turning and creeping much later in life. The psychological fears from exposure to light, behavioral symptoms including isolation, lack of social smile, gaze fixing, disturbed sleep and lack of recognition of faces

observed in the baby were related with neuropsychiatric disorders characterized by deficits in verbal communication, impairment of social interaction. A comparison of the symptoms of autism (Ma *et al.*, 2009) with this particular genotype revealed that the latter resembled in most of the aspects. The baby in the present case showed defective neurological development characterized by lack of social interaction, language, communication, verbal intelligence and deficits in interest and behavior (CDC, 2008). The spectrum of disorders was diagnosed before the age of 5 when he collapsed due to a severe fatal febrile seizure. Literature reports suggest that autism is highly heritable (Bailey *et al.*, 1995) however, in this particular case while the mother had a normal set of chromosomes, the father's chromosomal analysis showed translocation between chromosome 5p13 and 10p14. This might be the basis of phenotypic discordance observed in the baby.

Presently, investigations on relation of disorders and syndromes with genes are conducted as a routine. The scope of these researches is to pinpoint the impact of interactions between different genes on the same locus or different loci in addition to the impact of epigenetic factors (Zhang *et al.*, 2011). The genome region 5p13-15 in different syndromes including CDC, Autism and ASDs has many similarities in the clinical presentation with the present case whose specific deletion is 5p14. The interactions of genes and influence of epigenetic factors might protect or potentiate a particular clinical feature which might alter the very basis of that character (Wilk *et al.*, 1999). Hence, there is need to isolate the interactions and epigenetic factors to single out the clinical symptoms corresponding to the specific genomic region.

CONCLUSION

The clinical presentation of the present case is attributed to deletion at 5p14. Most of the symptoms of syndromes CDC, Autism and ASDs are common with the genomic region 5p14 besides some of the symptoms observed also corresponds to the other genes present in these syndromes. The discordance in phenotypic appearance might be related to the interactions between the genes at other loci and epigenetic factors. Literature studies today point to the genetic disorders and syndromes as the outcome of several genes, their interactions and also the environment. This may sound, improbable but the reversal of genetic disorders and syndromes might come up by the interactions between the genes and/or with the environment.

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