Close-kin marriage – An injustice to forthcoming generations

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ABSTRACT

Consanguineous marriage is the union between two individuals who are related as second cousins or closer and who have a common ancestor. There are various contributing factors to these marriages, namely, economic, cultural, social factors, and cultural isolation. Many societies nowadays do not allow marriages between close relatives, perhaps as a result of observations on the progeny of consanguineous marriages and the fear of unhealthy offsprings. This review article mainly intends to throw light on the genetic abnormalities caused by consanguineous marriages. It aspires to reveal the mystery behind the uncut diamonds sparkling as healthy children.

Key words: *Autism spectrum disorder, Cerebral palsy, Cleft lip and palate, Consanguineous marriage, Down's syndrome, Epilepsy*

The marital union among close biological kin is referred to as consanguineous marriage. In clinical genetics, it is called the relationship between the first and second cousins by marriage [1]. Consanguinity facilitates homozygosity mapping in some of the inherited genetic disorders that are transferred as autosomal recessive in carrier individuals and appears in their offspring as congenital anomalies [2]. Consanguineous marriages are particularly prevalent in Middle East and Southeast Asian countries, namely, Pakistan, South India, Bangladesh, and Sri Lanka, accounting for close to 50% of marriages in parts of Saudi Arabia and Pakistan [3]. National Family and Health Survey (1992) showed a higher prevalence of consanguineous marriage in South India compared to the other parts of India, and the difference is significant till date [4]. Literature shows a significant differences in genetic disorders between children born to consanguineous marriage partners and those born to non-consanguineous parents [5]. This review article throws light on the various ill effects of the consanguineous marriage.

CLEFT LIP (CL) AND CLEFT PALATE (CP)

CL and CP, also known as orofacial cleft, are a group of conditions that include CL, CP, and both together (CLP). According to the World Health Organization (2011), oral clefts occur in about 1 in every 700 live births and 31.8% of CL±P infants were the result of consanguineous marriages [6]. It can occur due to many etiological factors such as single mutant genes, chromosomal aberrations, specific environmental agents, and by the interaction of many genetic and environmental differences (the great majority), each with a relatively small effect (the multifactorial group) [7]. In an epidemiological study, Elahi *et al*. (2009) [8] unveiled a relatively higher incidence (32%) of consanguineous marriages in the parents of children with CL and/or CP in comparison with matched controls (18%). First-cousin marriages were more commonly implicated than the second-cousin marriages. A family history of cleft anomalies was present in 18 of 106 cases reviewed.

In a hospital-based, case–control study carried out in Rio de Janerio, Gonçalves *et al*. (2009) [9], disclosed the fact that the history of oral clefts either in the father's or in the mother's family was strongly associated with both CL±P, but parental consanguinity was associated only with CL/P. Aquino (2011) [10], in his retrospective study on craniofacial deformities, observed around 6.1% patients with non-syndromic type CL/P had a family history of first-degree consanguinity. CLP (unilateral or bilateral) was more frequent in males in the group of first-degree consanguinity. In a study conducted at Riyadh, Ravichandran (2012) [11] reported family history of clefts in one-third of patients out of 1171 CLP patients and consanguineous relationships were seen in 56.8% of their parents. Family history was more likely to be positive for patients whose parents were consanguineous than those who were non-consanguineous, both for the CL±P and CP groups.

Shawkya *et al*. (2013) [4] unveiled that 28.4% of parents with CLP children had a history of consanguineous marriages. Alamoudi *et al*. (2014) [12] in a retrospective study carried out in six hospitals in Jeddah, summarized that consanguinity among parents CP cases was statistically higher than that among CL with or without CP patients. Although there appears to be a trend in the relationship between consanguinity and severity of CL/P subphenotype, consanguineous parents were statistically higher

among CP cases. The prenatal diagnosis of CL and palate is done through obstetric ultrasonography which aids in the prenatal detection of facial anomalies by providing a new fetal dental panorama [13].

DOWN'S SYNDROME (DS)

DS, also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21 [14]. It affects up to 1 in 1000–1100 live births worldwide and affects 15% of people with learning disabilities [15,16]. The incidence is related to both genetic and environmental challenges [17]. The risk factors associated other than consanguinity include advanced maternal age, smoking, alcohol consumption, and drug abuse during pregnancy. Alfi *et al*. (1980) [18] evaluated the data on factors associated with the occurrence of DS in a highly inbred population in Kuwait to investigate the presence of a genetic sway in man. He observed an increased frequency of consanguineous parents among their DS patients and postulated the existence of a gene that could influence mitotic non-disjunction in the zygote. A possible explanation for this was that the consanguinity is usually perpetuated in certain families, or sections of the population, and parents in highly inbred families have a higher probability to be homozygotes for that gene.

Stoll *et al*. in 1990 [19] studied the epidemiology of DS among 139 new DS cases during the period of 1979–1987. More than 50 factors were evaluated and compared to those from control infants. According to them, there were 7.9% of consanguineous marriages associated with DS. Muller *et al*. (2001) [20] observed a significant effect of consanguinity among patients with chromosomal abnormalities. Down syndrome, esophageal atresia, and profound deafness were the common malformations/disorders associated. The rate of malformations and significant medical conditions were 7.77% when the parents were first cousins and 3.63% when they were not related. Amudha *et al*. (2005) [21] observed a significant effect of consanguinity on chromosomal abnormalities. They added that chromosomal abnormalities, numerical, and structural may occur as *de novo* at post-zygotic mitosis or transmitted because of the errors at meiosis in the parental gametogenesis.

Hamay *et al*. (2011) [22] inferred that on an average, when the first cousins were married, there is a 1.7–2.8% extra risk of having a child with an autosomal recessive disorder. Shawkyaetal (2013) [4] reported 28.8% incidence of DS in children whose parents were consanguineous. Similarly, Islam (2017) [23] also reported that consanguineous marriages are the main cause of DS in Oman region. Ray *et al*. (2018) [24] from his comparative analysis between non-consanguineous (n=811) and consanguineous (n=157) marriages concluded that consanguinity is a novel risk factor associated with the increase in the risk of chromosome 21 non-disjunction in families. Early diagnostic and screening tests during pregnancy identify a baby with DS. Soft-tissue markers such as small or no nasal bone, large ventricles, and nuchal fold thickness aid in the diagnosis of DS through ultrasound generally at 14–24 weeks of gestation. Increased fetal nuchal translucency indicates an increased risk of DS. In addition, rapid molecular assays such as fluorescent *in situ* hybridization, quantitative fluorescence polymerase chain reaction, and multiplex probe ligation assay and amniocentesis are also used for prenatal diagnosis [25].

EPILEPSY

Epilepsy represents a spectrum of brain disorders with recurrent seizure caused due to the inborn brain malformations and altered metabolic states. Disturbance in normal pattern of neuronal activity, abnormality in brain wiring, and imbalance in neurotransmission lead to epilepsy which, in turn, causes impeded motor and sensory function. Risk factors for developing epilepsy include severe head injury, seizures in the 1st month of life, use of illegal drugs such as cocaine, and brain tumor. At the global level, it is estimated that nearly 70 million people suffer from epilepsy and the prevalence is about 5–9 per 1000 population. Consanguineous marriages might have potentiated the tendency of familial aggregation of convulsive disorders. However, the effect and influence of consanguineous marriage on epilepsy remain contentious and under intense investigation [26].

Ramasundrum and Tan (2004) [27] observed an increased risk for epilepsy among siblings of patients with idiopathic and cryptogenic epilepsy. They also had a history of parental consanguineous marriage. In addition, there was an increased risk of epilepsy in the children of those with cryptogenic epilepsy. Asadi-Pooya (2005) [28] also observed significantly higher percentage of consanguinity in parents of the epileptic patients in comparison to a sample of the general population, which signifies the importance of consanguinity as a potential risk factor for epilepsy. In a study by Shawkya *et al*. (2013) [4], 42.5% of epileptic children had parents who were related in consanguineous marriages. Chentouf *et al*. (2014) [29], in their case–control study, identified five factors which were significantly associated with epilepsy, among which first-degree consanguinity was the primary one. In a whole genome sequencing in 404 predominantly consanguineous Iranian families, 28% were affected by epilepsy [30].

Alanazi *et al*. (2018) [31], in their study among North Saudi Arabian population, reported a significant association between consanguinity and epilepsy. Around 59.1% of epilepsy patients who participated in the study had parents who were cousins and 68.2% of epilepsy patients who participated in the current study had positive family history of epilepsy. In a Malaysian cohort (n=2100) affected by genetic generalized epilepsy, a substantial proportion had positive family history [32]. The implementation of a strategy for prevention and awareness of the impact of consanguineous marriages as well as genetic counseling for couples with a family history of epilepsy is needed. The use of ultrasonography to diagnose abnormal fetal movements, including fetal seizures, can better prepare the parents and clinicians for delivery of a neurologically impaired neonate. Further, the ultrasonography can provide evidence that abnormal behavior

predates the birth procedure, which will decrease the legal risk for the obstetrician. It is also essential to perform detailed imaging studies of the brain in the presence of fetal seizures to understand the etiology and to predict the risk of recurrence [33].

AUTISM

Autism is a common neurodevelopmental syndrome with a strong genetic component. The study of autistic individuals whose parents are cousins highlights the genetic diversity of this condition [34]. Based on epidemiological studies conducted over the past 50 years, there is increase in the prevalence of autism spectrum disorder (ASD) worldwide, with every 1 in 160 children are diagnosed with ASD. Morrow *et al*. (2008) [35] in his study described a genetic basis of the disease. The other risk factors include extreme preterm babies, fragile X syndrome, benign tumors in the brain, Rett syndrome, and family history of autism. The ASD had significant association with level of consanguinity when compared with controls, with an increased risk of 3.22 with consanguineous parents [36]. This raises the possibility of recessively inherited genetic risk factors for the etiology of ASD. Consanguinity is reported to have serious effects on fetal growth and development and increases the risk of congenital malformations [37].

According to the Homozygosity Mapping Collaborative for Autism, individuals with related parents are more likely to have inherited causes of the autism [34]. Saleh *et al*. (2009) [38], in their study on 49 children with ASD in Saudi Arabia, reported that 14 patients had consanguineous parents. Similarly, another Saudi Arabian study by Oommen *et al*. (2018) [39] also reported that 52% of the autistic children had parents with a history of consanguineous marriages mostly first-cousin marriages. Morrow [34] stated that cherry picking consanguineous families are a fruitful path to identifying autistic genes. Although definitive prenatal diagnostic tests are not available for autism, ultrasound scans that went on to check for fetal defects showed that children who went on to develop ASD, had greater head and abdominal sizes at around 20 weeks of gestation in the womb than did their healthy peers. It opens a wide range of possibility in the field of research if ASD is detectable this early on.

CEREBRAL PALSY (CP)

CP is a group of involuntary movement disorders that appear in early childhood. Signs and symptoms vary among people and include poor coordination, muscle stiffness and weakness, tremors, problems with sensation, vision, hearing, swallowing, and speaking. The prevalence of CP ranges from 1.5 to 4 per 1000 live births. The previous studies have reported that one of the major causes of death in fetuses and infants was abnormalities and disabilities [40-44]. Daher *et al*. (2014) [45] in his case–control study investigated risk factors for CP in a Palestinian population and observed a positive association between consanguinity and birth deficits in other family members and CP suggesting a possible genetic link. Having consanguineous parents increased the risk of CP almost 3-fold (odds ratio = 2.85) and having other children with disabilities in the family increased it almost 9-fold.

A pilot study conducted in Karachi reported that around parents of 50% of children with CP had a history of consanguinity [46]. Studies of Pakistani Muslim families living in Britain show that while the rate of CP may [47] or may not be higher overall, the risk of CP among offsprings of consanguineous marriages is very much increased with the rate of almost 1% [48]. Shawkya *et al*. (2013) [4] in his study observed that parents of 36.7% of patients with CP patients had a history of consanguineous marriage. The other risk factors include low birth weight or preterm birth, infertility treatments, multiple gestations, infections or fever during pregnancy, exposure to toxic chemical during pregnancy, jaundice, seizures, complicated labor and delivery, and Rh incompatibility between mother and fetus. Although there is no definitive prenatal diagnostic test for CP, good medical care during pregnancy and child birth can help to reduce the risk.

CONCLUSION

Consanguinity is a deep-rooted social trend with 1 billion people currently living in countries where consanguineous marriages are customary, and among them, one in every three marriages is between cousins. The rising public awareness of possible preventive measures for congenital disorders has led to an augmentation in the number of couples seeking preconception and premarital counseling on consanguinity. Hence, consanguineous couples can be identified, provided with the necessary information about their risk and, if needed and wanted, referred for genetic counseling. As goes the saying of Nelson Mandela, “It always seems impossible until it is done,” let’s do some justice to the future generation by igniting their minds about close-kin marriage.

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