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MARRIAGE PATTERNS AND PEDIATRIC NEUROLOGIC DISEASE IN DAMASCUS, SYRIA

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ABSTRACT

Aim: The aim of this study was to correlate the presence of neurologic disorders in Syrian children with parental consanguinity and investigate the cultural patterns which result in endogamy. **Methods:** We examined 128 patients and 132 control children who were matched for age, sex, and place of residence. Parental marital patterns were established. **Results:** Consanguineous marriages were seen in 62.5% of the case group and 33.3% of the control group (P=0.006). Patients were classified into 6 groups: (1) seizure disorder (n=22); (2) developmental delay (n=35); (3) seizures and developmental delay (n=20); (4) neurometabolic disorders (n=29); (5) CNS malformations (n=14); and neuromuscular or spinocerebellar disorders (n=8). Consanguinity was a risk factor for development of neurologic disease in the following categories: developmental delay (p=0.003), seizures with developmental delay (p=0.018), neurometabolic degenerative disorder (p=0.0001), and CNS malformations (p=0.035). Inbreeding coefficients calculated for these subclasses gave similar findings. The inbreeding coefficient (F) for the cases group is 0.0312 and for the control group is 0.0147. **Conclusion:** Endogamous marriages carry a considerably high risk for developing neurologic diseases.

Endogamy (marriage within a specific tribe or other social unit), especially consanguineous marriage, is common in Asia and Africa, despite its associated risk of autosomal recessive diseases in the offspring. The topic of endogamy has rarely been discussed in the pediatric literature. Limited epidemiologic and anthropologic literature has provided sources of information about endogamy. In this study we sought to determine the prevalence of endogamy in our pediatric neurology patients; we also reviewed the rationale for endogamous marriages in the Arab and Muslim communities.

Two international trends make it imperative that physicians all over the world must appreciate the prevalence and bases of endogamy - the growing transnational migration of large populations, especially out of Asia and Africa, and the increase in international medical consultation. Consanguineous families are thus increasingly seen for medical care at centers where they may have been seldom encountered previously.

METHODS

Study subjects were children from birth to 12 years of age who were referred for neurologic evaluation to the child neurology clinics at Damascus Children's Hospital (DCH) between September 1992 and June 1993. We limited our cases to Arab Muslim children living within a 30 km radius of the center of Damascus. This was necessary since specialty clinic populations might be drawn from wider geographic areas (and perhaps socioeconomic strata) than the control population, which included children from the general outpatient clinic at the DCH. Only one child per family was included. We did not control for socioeconomic variables.

Children whose neurologic disease was acquired by prenatal injury, infection, vasculitis, tumor, trauma, or endocrinopathy, were excluded from the study. The remaining study population comprised children whose CNS disease was likely caused by congenital or genetic etiologies, or which could reasonably be considered idiopathic. A total of 128 children fulfilled the criteria.

TABLE 1

Comparison of Cases and Controls

	Cases	Controls	p value
Ages (years ± S.D.)	4.5 + 3.5)	4.2 + 3.5)	0.53
Sex (% male)	60.2	53.0	0.23
Residence			
(% Damascus)	56.3	44.7	0.58
(% Outside Damascus)	53.0	47.0	
TOTAL	**128**	**132**	**--**

A diagnostic clinical classification was made for each case based on standard neurologic history and physical examination. In the absence of laboratory and imaging facilities, classification was strictly on clinical grounds. Cases were grouped into one of the following categories: isolated seizure disorder; isolated motor, speech, hearing or visual developmental delay; seizure disorder and developmental delay; neurometabolic degenerative process; CNS malformation; and neuromuscular or spinocerebellar disorders.

Parents' marital pattern was established and assigned to one of the following categories: no blood relation; first cousins; second cousins; or, distant cousins. The last-mentioned category was rare and these responses were clustered together with second cousins. The rationale for this was that any inbreeding coefficient would probably significantly underestimate consanguinity, since ancestral relationship prior to the children's parents was not studied in these families.

Controls were gathered from the DCH Outpatient Clinic during the same nine-month period. This clinic sees mostly children from in and around Damascus. Usually the children are seen for well child visits, or for common and benign pediatric complaints. On random days we collected information on consecutive children, ages birth to 12 years, seen in the clinic. Children with genetic disorders, histories of current neurological complaints, or those with developmental delay were excluded as controls. Recruited was limited to Muslim Arab children living within a 30 km radius of central Damascus. Only one child per family was included. Parental marital patterns were assessed in the same manner as for cases.

Group comparisons were analyzed using Student's t test, Chi square test, and Fisher's Exact test, as applicable. Marriage patterns of cases living within and outside Damascus were compared by Chi square analysis. Odds ratios and their 95% confidence intervals (CI) were calculated. A standard measure of inbreeding, the inbreeding coefficient (F), was calculated for both the overall case group and controls, and also for individual neurologic diagnostic groups. The inbreeding coefficient is defined as the probability that the two genes present in an individual at a given locus are identical by descent. It is a measure of kinship or parentage.[1,2]

RESULTS

A total of 128 cases and 132 controls were studied. Cases and controls were matched for age, sex and place of residence (Table 1). Consanguineous marriages were

TABLE 2

Parental Martial Patterns in cases and controls by Neurological Diagnosis

	No.	Without consanguinity (%)	With first cousin consanguinity (%)	With any consanguinity (%)
1. Seizure Disorder	22	59.1	13.6	40.9
2. Developmental Delay	35	40.0	42.9	60.0
3. Seizures/ Developmental Delay	20	40.0	45.0	60.0
4. Neurometabolic Degeneration	29	13.8	72.4	86.2
5. CNS Malformation	14	35.7	57.1	64.3
6. Neuromuscular/ Spinocerebellar Degeneration	8	50.0	25.0	50.0
CASES (Total)	**128**	**37.5**	**45.3**	**62.5**
CONTROLS (Total)	**132**	**66.7**	**20.4**	**33.3**

TABLE 3

Ods Ratios (with 95% CI and P values) according to Parental Martial Patterns

Diagnostic category	OR (95% CI) First Cousins	P value	OR (95% CI) Any Consanguinity	P value
1. Seizure disorder	0.61(0.13-2.43)	0.45	1.43(0.52-3.94)	0.45
2. Developmental delay	2.921(1.29-6.93)	0.007	3.10(1.36-7.19)	0.003
3. Seizures/ Developmental delay	3.18(1.08-9.37)	0.016	3.1(1.08-9.08)	0.018
4. Neurometabolic degeneration	10.2(3.77-28.47)	0.0001	12.94(3.93-47.05)	0.0001
5. CNS malformation	5.19(1.47-18.72)	0.005	3.72(1.05-13.74)	0.035
6. Neuromuscular/	1.30(0.17-7.74)	0.67	2.06(0.41-10.47)	0.44

seen in 62.5% of the case group and 33.3% of the control group (P=0.000006). The distribution of patients in various subcategories was as follows: seizure disorder, n=22; developmental delay, n=35; seizures and developmental delay, n=20; neurometabolic disorders, n=29; CNS malformations, n=14; and neuromuscular or spinocerebellar disorders, n=8 (Tables 2 and 3). The calculation of odds ratios with 95% confidence intervals and p values using consanguinity as a risk factor for development of neurologic disease was as follows: seizure disorder, p=0.45; developmental delay, p=0.003; seizures with developmental delay, p=0.018; neurometabolic degenerative disorder, p=0.0001; CNS malformations, p=0.035; and neuromuscular or spinocerebellar disorder, p=0.44 (Table 4). Inbreeding coefficients for these subclasses gave similar findings. The inbreeding coefficient (F) for the case group is 0.0312 and for the control group is 0.0147 (i.e., 2.12 times higher in cases than in controls, see Table 5).

DISCUSSION

Our results reveal that the families of children with neurological disease had a markedly elevated rate of consanguineous endogamy. First-cousin marriage was most common. Inbreeding coefficient in the case population was more than double that of the control group. The control group's coefficient was 184 times higher than that estimated for the general US population. Certain neurologic diagnostic groups, as would be expected, revealed especially elevated odds rations suggesting consanguinity as an associated factor, or by looking at first-cousin marriage alone as a risk factor. Children in these diagnostic groups also had correspondingly high inbreeding coefficients, as would be expected. Overall, 62.5% of the children studied were products of consanguineous marriages, with the highest rate (86%) seen in children with neurometabolic disorders. This is in contrast to the control group, which had 33.3% parental consanguinity. Children with seizure disorders (n=22) had no increased odds for consanguinity as a risk factor, and the inbreeding coefficient in this group was nearly identical to that of the control population. This finding is consistent with other reports.[3, 4]

It would be expected that children with neurometabolic degenerative processes would be more commonly born into endogamous families, since most of these disorders are autosomal recessive. Many of the children grouped under developmental delay may have been inadvertently misclassified; some may represent cases more typical of neurometabolic degeneration. The 15 children with CNS malformations may have genetic bases for their disorders, but typically CNS malformations (including spinal dysraphism) are not autosomal recessive. The 8 children with neuromuscular or spinocerebellar disorders would likely have genetic bases for their disorders, in many cases, autosomal recessive.

Powerful cultural reasons perpetuate endogamy (marriage into the same clan or kinship group) throughout the world. These include economic, religious, familial and political reasons. Economic reasons have been among the strongest, as endogamy is effective in slowing down fragmentation of family land and property. A further economic advantage of endogamy is that the bride's price is much less when the woman is from within the family. Economically and politically, endogamy reinforces strength of lineage and prevents its fission.[5]

The religious basis of endogamy is less clear. Pre-Islamic religion, especially in Persia, appeared to encourage endogamy.[6] Although commonly practiced among

TABLE 4

Inbreeding Coefficients (F) by Neurologic Diagnosis, with Control Comparisons

Neurologic diagnosis	Inbreeding coefficient
1.Seizure Disorder	0.0142
2. Developmental delay	0.0341
3. Seizures and Developmental delay	0.0304
4. Neurometabolic degeneration	0.0474
5. CNS malformation	0.0368
6. Neuromuscular/ Spinocerebellar degeneration	0.0195
Cases (overall)	**0.0312**
Controls	**0.0147**
U.S. Population	**0.00008**
U.K. Population	**0.000025**

Muslims, there is no clear-cut religious teaching in the Quran to support the practice. The traditional rationale of "cousin-right" is powerfully accepted in many rural areas of the Middle East. Also, a common rationale for endogamy is the widely accepted belief that endogamy reduces problems with the in-laws. In addition, it became clear during our study that a thorough knowledge of the prospective spouse and family is a prerequisite for marriage in Syrian society. This opportunity for careful screening of the future marital partner may counterbalance the adverse effects of consanguinity in Middle Eastern cultures. It was noted that low educational attainment was a factor for endogamous marriages.[7]

A recent data reveals that the nations with the highest rates of endogamy are Kuwait (54%), Jordan (41%), Lebanon (25%), Algeria (23%), and Egypt (22%), which contrasts with low rates in nations such as Japan (5-6%) or Brazil (2-3%). India and Israel have endogamy rates within local groups ranging from 1% to 15-20%.1 Khoury has reported that Syria has a consanguinity rate of 33%, the same figure found in our control population (33%). Counseling endogamous families who have had one or more children with autosomal recessive disease is not a simple exercise in educating them about Mendelian genetics. Dogmatic statements about endogamy and prohibition of future pregnancies are not adequate educational devices. Given social mores, divorce of the woman may be more likely the outcome of such interventions than the intended family planning. Finally, it should be pointed out that in our society many practicing physicians are married to their first cousins. In 1992, we surveyed 250 graduating Syrian medical students at the University of Damascus and found 15% of them were products of first- or second-cousin marriages. Genetic counseling by these physician groups may be made more difficult because of this.

One the most comprehensive studies of inbreeding and reproductive outcomes was reported from a ten-year study of births in Karnataka State in southern India.[2] Of 107,518 marriages, 31.4% were consanguineous. Consanguinity was most prevalent among Hindus (33.5%), who also had the highest coefficient of inbreeding (F=0.0333), because of the prevalent custom of uncle-niece marriages. Among Muslims in Karnataka, 23.7% marriages were consanguineous (F=0.0160).

Compelling data on the relationship between consanguinity and neurologic disability concerns hearing impairment. Feinmesser, Tell and Levi have produced a series of studies of Arab and Jewish children living in Israel. Consanguinity appears to be a major cause of sensorineural hearing loss when no other etiology can be found.[8] Over a 20-year period, they have described a significant decline in consanguinity as a cause of deafness in both Ashkenazi, Asian-African and Jewish populations in Israel.

Extensive studies of neurometabolic and genetic CNS disorders have been reported from Saudi Arabia and Kuwait.[9,10] Whereas in Western cultures, about one child in 1,000 births is affected by an autosomal recessive metabolic disorder, in Saudi Arabia approximately one in 50 births results in a diagnosable neurometabolic condition.[11,12] Ozand et al described 910 Saudi children referred for evaluation of neurologic disease.[12] A definite etiology was assigned to 52%; nearly all were autosomal recessive metabolic degenerative CNS disorders. Five Saudi tribes constituted 26% of the diagnosable burden of CNS metabolic degenerations. There have been reports of severe mental retardation in Jordan, and cerebral palsy in Saudi Arabia, being associated with consanguinity. In both cases, high rates of similar disease in siblings were noted.[13,14] Both papers suggested that neurologic morbidity was related to perinatal events, which in turn were related to parental consanguinity. It is likely that the children described in both studies more likely had degenerative rather than static neurologic processes, since both studies were retrospective, at least in regards to the younger age at the time of the first live birth. Greater morbidity and mortality was also found in this group.

A wide variety of other pediatric neurologic diseases including spinocerebellar degeneration, congenital insensitivity to pain, Wilson's disease, genetic visual loss, spinal muscular atrophy, and congenital myasthenic syndromes have been described in consanguineous populations in the Middle East and South Asia.[15-20]

CONCLUSION

Endogamous, especially consanguineous, marriages are a frequent occurrence in many parts of Africa and Asia. Although the practice is declining, especially in urban areas, the absolute number of such marriages and their offspring is probably increasing. Cultures in which endogamy is commonplace will increasingly bear the disproportionate burden of genetic disease in children; the discrepancy can be expected to become more noticeable as the large burden of child morbidity and mortality from acute infectious diseases is reduced. An appreciation of cultural factors promoting and sustaining endogamy in many populations should be balanced with the knowledge of its potential adverse genetic consequences.

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