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Original article

Epidemiology of congenital anomalies in the Kurram Tribal Agency, northwest Pakistan

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Background: We know of no study reporting hereditary and congenital anomalies (CA) prevalent among northwestern populations in the Federally Administered Tribal Areas (FATA) of Pakistan, a region of war and geopolitical unrest.
Objectives: To determine and report the epidemiology of CA in the Kurram Tribal Agency in northwest Pakistan.
Methods: A cross-sectional clinical and genetic epidemiological study was conducted in relatively safe pockets of the Kurram Agency of FATA and individuals or families with CA were randomly recruited through door-to-door surveys and visiting public places like the *Jirgah* and hospitals.
Results: This study ascertained 246 independent families or individuals with CA. They were grouped into 9 major and 49 minor phenotypic categories. Among the major categories, neurological disorders were the most frequent (n = 83; proportion = 0.337; CI = 0.278, 0.397), followed by musculoskeletal defects (n = 56), limb anomalies (n = 52), sensorineural/ear defects (n = 18), ectodermal anomalies (n = 11), congenital heart defects (n = 10), and eye/visual impairments (n = 6). Sporadic occurrence of anomalies was more frequent than familial occurrence (169 vs. 77), and isolated presentations were more common than syndromic appearance (170 vs. 76). The distribution of various ascertainment types (e.g. sex-wise, familial/sporadic, isolated/syndromic presentations), with demographic variables such as age, origin, ethnicity, education, family type, and parental consanguinity were mostly not significant.
Conclusions: Neurological disorders were the most frequent type of congenital anomalies in the Kurram Federal Tribal Agency of Pakistan.

Keywords: Congenital anomalies, descriptive epidemiology, FATA, genetic disorders, Pakistani

Childhood mortality and morbidity have declined in many countries and a shift has been observed from infectious diseases to chronic and hereditary diseases and congenital anomalies. Epidemiological transition has been shown a waning of infectious and acute diseases and the emerging importance of chronic and degenerative diseases. High mortality from infections is generally attributed to poverty, low socioeconomic circumstances, and limited infrastructure, which are wide-spread in the developing countries including the region selected for this study. Although developing countries still experience high infant and child mortality from infectious diseases, one of the major epidemiological trends of the present century is the rise of degenerative and chronic diseases and noncommunicable disorders [1, 2].

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Congenital anomalies (CA) constitute one of the largest fractions among the noncommunicable disorders in many societies and are a leading cause of prenatal losses and childhood morbidity and disability. CA affect a significant fraction of newborn populations and contribute to mortality and hospital admissions. An estimated 8 million children are born with a major birth defect annually, 3.3 million children with birth defects do not survive, and 3.2 million who survive may develop certain types of disability later in the life [3]. CA differ widely in their etiologies and prevention is possible in 60% of cases [4]. However, detailed studies on the epidemiology, risk factors, and distribution of CA are prerequisite for launching intervention programs.

The worldwide prevalence of CA has been estimated to be 4%-5%, but the actual numbers vary among countries and among regions [5]. Management of CA represents a challenge and requires a broader understanding of the problem.

In Pakistan, there is a paucity of data on the epidemiology of CA. Few of the representative studies have been conducted in a hospital-based setting, while population-based studies are largely missing [6-9]. Large scale epidemiological studies are difficult to conduct because of inadequate resources, lack of trained and skilled enumerators, and the long time required to complete such studies [10, 11]. The northwestern areas of Pakistan, particularly at the border of Pakistan and Afghanistan are remote and inaccessible, and it is quite challenging to conduct any study in those areas. The unique geopolitical situation and certain demographic and military events taking place make the free movement of researchers extremely difficult [12-14]. Further, the 'War-on-Terror' in the past decade has not only destroyed the basic infrastructure, socioeconomic, and educational institutions, but has also greatly impacted the psychological and mental well-being of the local population [15]. To our knowledge, there is no study of the pattern of congenital and hereditary anomalies prevalent in Federally Administered Tribal Areas (FATA) of Pakistan. With the help of local resource persons and tribal heads, we collected the first data on commonly occurring CA. Exploring further the spectrum of anomalies in this tribal area would be interesting, because most of the tribal groups are descended from a limited number of ancestors of Afghani origin.

Subjects and methods

Study population

A descriptive clinical and genetic epidemiological study was conducted in the Kurram Agency (KA), an area of the FATA at the northwestern border of Pakistan. According to the Pakistan Census of 1998, it had a population of 448,310 [16]. The KA is socioeconomically deprived area with inadequate health and educational facilities. The number of individuals per medical doctor is 6,728. The literacy rate ranges from 8% for women to 34% for men. Most people are involved in agriculture and livestock-rearing. Women take an active role in agriculture and collection of wood for fuel [16].

Sampling strategy

Before commencement, the present study was approved by the Ethical Review Committee of the Quaid-i-Azam University, Islamabad (reference DAS/13-HG6). Before launching the field-work, the study was approval by the local *Jirgah* and tribal elders (*Maliks*), who are authorized by the political administration to safeguard the area and resolve disputes among tribesmen. They had to be assured before start of the study that there were to be no breeches of an ethical nature or confidentiality. Data were obtained by door-to-door surveys and by visiting the *Jirgah* and Central District Hospital between July 2013 to May 2014. All the data were acquired and documented in writing with the help of community representatives after participants had provided their informed written or formally documented verbal consent when illiterate. When a participant was below the legal age of providing consent, or was incapable of providing it because of a disability (deaf, blind, mute), or otherwise incapable, a parent, guardian, or literate elder provided written informed or formally documented verbal consent after written or documented verbal assent was provided by the participant. Information regarding sociodemographic variables, consent and assent was documented on a structured form. Clinical data were acquired with the assistance of resident doctors [11]. Previous medical records and laboratory or pathological assessments were also recorded, when available.

Classification of anomalies and statistical analyses

We included only those anomalies that were congenital and/or hereditary presentations, while conditions of a traumatic or acquired/infectious nature were not considered. For each case, a detailed pedigree was constructed; however, only the index subject from each family was included in the data analyses. For the broader diagnosis of anomalies, we relied on the assessment provided by the specialist doctor at the District Hospital. To avoid bias the cases were thoroughly scrutinized by the same research team. All the anomalies were further classified according to the International Classification of Diseases criteria and closest definitions were also sought in the Online Mendelian Inheritance in Man database [17-19]. Syndromic cases were identified with respect to the more severe symptoms in the following order: neurological disorders, musculoskeletal, eye/visual anomalies, and limb defects.

Results

Sample characteristics

The study identified a total of 246 independent families or individuals having a certain type of CA. Among the index cases, there were 135 (54.9%) men or boys and 111 (45.1%) women or girls (**Table 1**). All the malformations evident among the recruited families could be resolved into 9 major categories. The sporadic occurrence of anomalies was customary compared to the familial nature; however, the distribution of sporadic and familial cases was highly variable among the CA ($P < 0.0001$). Furthermore, most of the CA had isolated presentations contrasting to syndromic appearance ($P < 0.0001$). Limb defects, sensorineural/ear and ectodermal anomalies were mostly isolated presentations (**Table 1**). Among all families, there were 493 affected individuals in total with higher propensity in affected male individuals.

Categories of congenital anomalies

All the CA were grouped into 9 major and 49 minor categories and their relative proportions were calculated (**Table 2**). Among the major categories, neurological disorders was the most frequent (34%), followed in descending order by musculoskeletal defects (23%), limb defects (21%), sensorineural/ ear defects (7%), ectodermal anomalies (4.4%), congenital heart defects (4%), and eye/visual impairments (2.4%) (**Table 1**). Further, the neurological defects were grouped into 13 subcategories, and among the most frequent were mental retardation, followed by Down syndrome (trisomy 21), and microcephaly. Among the 16 subcategories of musculoskeletal defects there was a higher representation of individuals with dwarfism and arthro-gryposis (**Table 2**).

Limb defects were represented by six distinct entities (**Tables 2** and **3**). Subjects with amputations/ limb deficiency were the most frequent, followed by polydactyly, clubfoot, syndactyly, brachydactyly, and clinodactyly, in descending order. Among these participants with phenotypic variability in limb anomalies (**Table 3**), there were 82 affected limbs, with the right arm was most frequently affected. In majority of the participants, only the upper limbs or only the lower limbs were involved.

Pedigree analyses of the familial cases demonstrated that the majority of the disorders segregated in 1 or 2 generations, while in some cases, especially of limb defects, the anomalies segregated up to 4 consecutive generations (**Table 4**). Similarly, in most of the familial cases the malformations affected 1 or 2 siblings, while in 10 kindreds, 5 or more siblings were affected. Among the sporadic anomalies, most of the index cases belonged to fifth or higher gravida, followed by individuals from a first pregnancy (**Table 5**).

The distribution of various sample ascertainment types (such as sex-wise, familial/sporadic, isolated/ syndromic presentations), with respect to demographic variables such as age-range, origin, caste/ethnicity, education, and family type were, mostly, not significant (**Table 6**). Further, parental consanguinity of the index participant was calculated as 55.3%. The familial cases were more likely to have parental consanguinity, and the distribution of familial/sporadic samples with respect to parental consanguinity was significant (**Table 7**).

Syndromic anomalies

Among the 65 syndromic malformations, 84 associated anomalies were identified. The majority of the syndromic malformations included cases of mental retardation and dwarfism. The most common associations observed were delayed milestones, squint eyes, digital defects, neuromuscular anomalies, and deafness/mute (**Table 8**).

Discussion

To our knowledge, the present research is the first of its kind in the remote Tribal Areas of Pakistan. The populations of Tribal Areas of Pakistan are geographically locked in mountainous regions, and in most part, deprived of socioeconomic and civic development. The ongoing geopolitical turmoil in the region has badly affected the existing facilities of health and education [12, 14]. Because of the poor infrastructure of health facilities and staff, systematic documentation of births and congenital anomalies are not available. This study is a pilot observational effort to screen the population of the Kurram Agency for the occurrence of commonly occurring congenital and hereditary anomalies.

Of the total 246 cases, neurological disorders including mental retardation were the most frequent (**Table 1**). Among the mental retardations, cases with mild intellectual impairment were common (36.9%), followed by moderate types (20.2%), and the severe types less frequently (4.8%). Mental retardation was more prevalent in male individuals than female

Table 1. Distribution of major categories of congenital anomalies, with respect to index cases, familial/sporadic nature, isolated/sporadic presentations, and total affected family members

Congenital anomaly	Index participant			Familial/sporadic nature*		Isolated/syndromic presentation*		Total affected in all families		
	Male	Female	Total	Familial	Sporadic	Isolated	Syndromic	Male	Female	Both
Neurological disorder	46	37	83	17	66	41	42	64	47	111
Musculoskeletal defects	29	27	56	23	33	31	25	53	52	105
Limb defects	28	24	52	13	39	46	6	66	57	123
Sensorineural/ear defects	9	9	18	13	5	18	0	36	25	61
Ectodermal anomalies	6	5	11	6	5	11	0	21	28	49
Congenital heart defects	6	4	10	1	9	8	2	6	5	11
Eye/visual impairments	5	1	6	1	5	6	0	9	5	14
Growth retardation	2	2	4	0	4	3	1	2	2	4
Others	4	2	6	3	3	6	0	9	6	15
Total	**135**	**111**	**246**	**77**	**169**	**170**	**76**	**266**	**227**	**493**

*differences in the distribution were statistically significant

Table 2. Major and minor categories of congenital/hereditary malformations observed in the studied population

Malformation (major/minor)	No. of cases	Proportion	95% CI	OMIM*	ICD-10*
Neurological disorders	**83**	**0.337**	**0.278, 0.397**		
Mental retardations	49	0.199	0.149, 0.249	300243	F03
Down syndrome	11	0.045	0.019, 0.071	190685	Q90
Microcephaly	6	0.024	0.005, 0.044	251200	Q02
Spina bifida	4	0.016	0.001, 0.032	182940	Q05, Q76.0
Cerebral palsy (unspecified)	3	0.012	-0.002, 0.026	605388	G80.9
Quadriplegia	2	0.008	-0.003, 0.019		G82.5
Spastic cerebral palsy	2	0.008	-0.003, 0.019	603513	G80.0
Ataxia telangiectasia	1	0.004	-0.004, 0.012	208900	G11.3
Cerebral atrophy	1	0.004	-0.004, 0.012		G31.9
Dystonic cerebral palsy	1	0.004	-0.004, 0.012		G80.3
Epilepsy	1	0.004	-0.004, 0.012	607208	G40
Psychoneurosis	1	0.004	-0.004, 0.012		F41.1
Schizophrenia	1	0.004	-0.004, 0.012	181500	F20
Musculoskeletal defects	**56**	**0.228**	**0.175, 0.280**		
Dwarfisms	19	0.077	0.044, 0.111	100800	Q77.4
Arthrogryposis	8	0.033	0.010, 0.055	108110	Q74.3
Hip dysplasia/dislocation	4	0.016	0.001, 0.032	42700	Q65
Spinal muscular atrophy	4	0.016	0.001, 0.032	253300	G12.1
Muscular dystrophy	3	0.012	-0.002, 0.026	310200	G71.0
Osteogenesis imperfecta	3	0.012	-0.002, 0.026	166200	Q78.0
Congenital dislocation of patella	2	0.008	-0.003, 0.019	169000	Q74.1
Congenital kyphosis	2	0.008	-0.003, 0.019		Q76.4
Congenital scoliosis	2	0.008	-0.003, 0.019		Q76.3
Ellis–van Creveld syndrome	2	0.008	-0.003, 0.019	225500	Q77.6
Vitamin-D resistant rickets	2	0.008	-0.003, 0.019	277440	E83.3
Congenital patellar syndrome	1	0.004	-0.004, 0.012	147891	Q74.1
Exostosis	1	0.004	-0.004, 0.012	133700	Q78.6
Hypotonia	1	0.004	-0.004, 0.012		P94.2
Nail-patella syndrome	1	0.004	-0.004, 0.012	161200	Q87.2
Pfeiffer syndrome	1	0.004	-0.004, 0.012	101600	
Limb defects	**52**	**0.211**	**0.160, 0.262**		
Amputations/deficiency	20	0.081	0.047, 0.116	217100	Q73.0, Q72.0
Polydactyly	12	0.049	0.022-0.076	603596	Q69.9, Q69
Clubfoot	8	0.033	0.010, 0.055	119800	Q66.89, Q66.0
Syndactyly	8	0.033	0.010, 0.055	609815	Q70.9
Brachydactyly	3	0.012	-0.002, 0.026	112500	Q68.1
Clinodactyly	1	0.004	-0.004, 0.012		Q74.0
Sensorineural/ear defects	**18**	**0.073**	**0.041, 0.106**		
Deaf-mute	17	0.069	0.037, 0.101	304400	Q18
Usher syndrome	1	0.004	-0.004, 0.012	276901	H35.5
Ectodermal anomalies	**11**	**0.045**	**0.019, 0.071**		
Ichthyosis	7	0.029	0.008, 0.049		Q80
Early tooth decay	2	0.008	-0.003, 0.019		K02
Albinism	1	0.004	-0.004, 0.012	300500	E70.3
Alopecia areata	1	0.004	-0.004, 0.012	104000	L63
Congenital heart defects	**10**	**0.0401**	**0.016, 0.065**		**Q20–Q26**
Eye/visual impairments	**6**	**0.024**	**0.005, 0.044**		
Anophthalmia	3	0.012	-0.002, 0.026		Q11.1
Blindness	2	0.008	-0.003, 0.019		H54.1
Squint eyes	1	0.004	-0.004, 0.012	231000	Q10
Growth retardation	**4**	**0.016**	**0.001, 0.032**		**Z00.70**
Other	**6**	**0.024**	**0.005, 0.044**		
Cleft palate	2	0.008	-0.003, 0.019		Q35
Bilateral ureteric reflux	1	0.004	-0.004, 0.012		N13.7
Metachromatic leukodystrophy	1	0.004	-0.004, 0.012	250100	E75.2
Thalassemia	1	0.004	-0.004, 0.012	613985	D56
Popliteal pterygium syndrome	1	0.004	-0.004, 0.012	119500	Q79.8

#First six categories employed a χ^2 test, *Online Mendelian Inheritance in Man, and International Classification of Disease–10 database identifier/Entrez number, CI, confidence interval.

Table 3. Pattern of limb defects in the studied cohort of individuals with congenital anomalies

Limb defects	No. of cases (n = 52)	Total affected limbs (n = 82)	Upper limb (n = 42)		Lower limb (n = 40)		No. of cases with involvement			No. of limbs involved			
			RA	LA	RL	LL	Arms only	Legs only	Both	Any 1	Any 2	Any 3	All 4
Amputation	20	28	14	10	1	3	16	1	3	15	2	3	0
Polydactyly	12	20	7	4	5	4	6	4	2	8	2	0	2
Clubfoot	8	12	0	0	5	7	0	8	0	4	4	0	0
Syndactyly	8	15	2	2	5	6	2	6	0	1	7	0	0
Brachydactyly	3	5	0	1	2	2	1	2	0	1	2	0	0
Clinodactyly	1	2	1	1	0	0	1	0	0	0	2	0	0
Total	52	82	24	18	18	22	26	21	5	29	19	3	2

LA = left arm, LL = left leg, RA = right arm, RL = right leg

Table 4. Number of disease segregating generations and affected siblings

Congenital anomalies	Disease segregating generations				No. of affected siblings				
	I	II	III	IV	1	2	3	4	≥5
Neurological disorders	13	3	0	1	8	8	0	0	1
Musculoskeletal defects	16	6	0	1	11	8	3	0	1
Limb defects	4	3	2	4	0	7	1	1	4
Sensorineural/ear defects	2	2	2	0	1	2	1	0	2
Ectodermal anomalies	7	5	0	1	5	3	3	0	2
Congenital heart defects	1	0	0	0	1	0	0	0	0
Eye/visual impairments	0	0	1	0	0	0	0	1	0
Growth retardation	0	0	0	0	0	0	0	0	0
Others	2	1	0	0	1	1	0	1	0
Total	**45**	**20**	**5**	**7**	**27**	**29**	**8**	**3**	**10**

Table 5. Sporadic cases: parity and size of normal sibships of affected subjects

Congenital anomalies	No. of cases	Parity of index subject (in No. of cases)						Size of normal sibships (in No. of cases)					
		1st	2nd	3rd	4th	≥5th	mean (SD)	0	1-2	3-4	5-6	≥7	Mean (SD)
Neurological disorders	66	16	5	11	8	26	4.24 (2.85)	2	11	17	14	22	4.84 (2.57)
Musculoskeletal defects	33	8	4	7	5	9	3.52 (2.29)	1	6	13	6	7	4.45 (2.56)
Limb defects	39	7	12	6	4	10	3.48 (2.44)	1	12	8	10	8	4.43 (3.04)
Sensorineural defects	5	2	0	0	1	2	3.40 (2.30)	1	2	1	1	0	2.40 (1.82)
Ectodermal anomalies	5	0	2	0	0	3	4.80 (2.95)	0	2	0	2	1	4.20 (2.77)
Congenital heart defects	9	2	1	2	2	2	3.56 (2.46)	1	3	3	1	1	3.22 (2.17)
Eye/visual impairments	5	2	0	0	1	2	4.60 (3.91)	0	0	2	3	0	4.40 (1.34)
Growth retardation	4	0	0	0	0	4	7.24 (1.25)	0	0	1	1	2	6.75 (2.50)
Others	3	1	1	0	0	1	3.33 (3.21)	1	0	1	1	0	3.00 (3.00)
Total	**169**	**38**	**25**	**26**	**21**	**59**	**3.94 (2.65)**	**7**	**36**	**46**	**39**	**41**	**4.49 (2.66)**

SD, standard deviation.

Table 6. Demographic distribution of index subjects

Demographic variables	Male	Female	Total
Age (years)			
≤9	52	38	90
10-19	49	49	98
20-29	17	9	26
≥30-39	17	15	32
Origin			
Rural	117	94	211
Urban	18	17	35
Total	135	111	246
Caste/ethnicity			
Turi	66	53	119
Bangash	38	40	78
Syed	18	13	31
Others	13	5	18
Economic status (parental)*			
Low	13	9	22
Low–mid	56	57	113
Mid	46	40	86
High–mid	20	5	25

*Differences in the distribution were significant

Table 7. Relationship of consanguinity and different sample ascertainment types

Variable	Parental marriage type		Total cases
	Consanguineous	Nonconsanguineous	
Sex			
Male	73	62	135
Female	63	48	111
Familial/sporadic nature*			
Familial	53	24	77
Sporadic	83	86	169
Total	**136 (55.3%)**	**110 (44.7%)**	**246**

*Differences in the distribution were significant

individuals (**Table 2**). This is in agreement with the findings of Amaral et al. [20], who showed in their cohort a great number of male individuals affected with mental retardation than female individuals, amongst which mild phenotypes were the most frequent, followed by moderate, and severe in that order. However, the prevalence of mental retardation varied according to the classification system used. Neurological disorders, including mental retardation, accounted for 34% of the total anomalies followed by musculoskeletal and limb defects, deaf-mute, skin anomalies, congenital heart defects, and visual defects in descending order. A study carried out by Dastigiri et al. [21] showed the incidence of limb defects as 15.1%, disorders of central nervous system 11.2%, musculoskeletal defects 7.6%, and eye and ear anomalies as 1.3% and 0.6%, respectively. A study carried out by Eluwa et al. [22] showed the highest representation of central nervous system anomalies (36.37%), followed by malformations of skeletal system (18.1%) and cardiovascular system (4.55%).

No significant association was observed between parental consanguinity and various categories of CA. However, the exceptions were congenital heart defects and deaf/mute cases where the parental consanguineous marriages predominated over the

Table 8. Syndromic cases with the combination of associated malformations

Major presentation	No. of cases	Associations										Total
		Delayed milestones	Squint eyes	Digit defects	Neuromuscular defects	Deaf/ mute	Scoliosis	Clubfoot	Blindness	Microcephaly	Nail atrophy	Others	
Mental Retardation	24	6	4	1	4	5		1	1	1		Bulging eyes (2), Epilepsy (3), Muscular dystrophy (3) Delayed puberty (1)	**32**
Dwarfism	12				1	1	2		1	1	1	Webbed neck (4), Ribs dislocation (1), Delayed puberty (1)	**13**
Microcephaly	6	1		1		1						Mental retardation (4)	**7**
Amputation	5			3	2		1	1					**7**
Down syndrome	4		1	4	1							Dental decay (1)	**7**
Osteogenesis imperfecta	3						1	1	1				**3**
Cerebral palsy	3	3	2										**5**
Congenital heart defect	2		1					1			1		**3**
Arthrogryposis	2		2										**2**
Clubfoot	1			1									**1**
Muscular dystrophy	1						1						**1**
Congenital scoliosis	1				1							Cleft palate (1)	**2**
Quadriplegia	1								1				**1**
Total	**65**	**10**	**10**	**10**	**9**	**7**	**5**	**4**	**4**	**2**	**2**	**21**	**84**

nonconsanguineous marriages. Previously, Liu et al. [23] and Ali [24] reported a significant relationship between deaf/mute cases and consanguineous marriages of the parents. A study conducted by Sharkia et al. [25], showed a remarkable effect of consanguinity on the prevalence of mental retardation.

There was a preponderance of index male individuals in the current sample. A number of previous studies have also documented male predominance amongst the congenitally malformed babies [26, 27]. Tennant et al. [28] reported that pregnancies affected by a birth defect, was more frequent in male fetuses than of female, i.e., 55% vs 45%, respectively. The present study found that there was overwhelming majority of CA that had sporadic presentations compared to familial occurrences. Further the sporadic cases primarily originated from rural areas. The higher prevalence of sporadic anomalies could be attributed to nongenetic and environmental factors specific to this area (discussed below), to which the pregnant women may be exposed [16].

Here, it can be further argued that a substantial number of sporadic cases may be the result of a higher rate of de novo mutation, which may be the result of specific factors in this territory. The FATA region at the Pakistan–Afghanistan border has been severely affected by warfare, and the fragile security conditions have forced a large number of families to migrate from one place to another, rendering drastic demographic changes and adverse impact on the health of inhabitants particularly children and women [15, 29]. A couple of studies have highlighted the negative consequences of war-on-terrorism on the local people of FATA [30, 15]. A substantial fraction of young children and women are victims of post-traumatic stress disorders and sense of insecurity. Furthermore, because of the continued warfare, it is quite likely that there has been an additional teratogenic effect because of contamination by environmental pollutants, residues from explosives, and heavy metals in the human food-chain. All these factors may have put pregnant mothers at a greater risk of birth defects.

FATA has been facing many problems in the form of conflicts, drone strikes, military operations and population displacements, which have rendered severe consequences on the physical, psychological and mental health of the masses, with women and children being the most vulnerable fraction [31]. A high prevalence of disorders including phobias, nightmares, stress, depression, and fear has been observed [15, 32]. The individuals who have experienced such situations adapt violent and aggressive behavior, and suicidal attempts have become common. Around 757,996 people have been displaced because of the war ongoing since 2008.

Although women are the most affected by this mass displacement, with many are suffering from anxiety disorders, panic disorders, mixed anxiety depression disorder and depression; studies have found that women's health is traditionally neglected in FATA. Even though the women are actively involved in outdoor activities, working in agriculture with their male family members, collecting wood for fuel and carrying water from springs located at the mountain side, there are inadequate health facilities available to them [16, 32, 33]. There are very few female doctors and health workers in FATA. In the rural areas, if a woman falls ill the male family members consider it shameful to bring her to the nearby city hospital. Most of the tribal elders do not allow their female tribal members to visit male doctors [16, 33]. The FATA Multiple Indicator Cluster Survey (MICS) demonstrated that only 50% of the population of Kurram Agency had access to improved sources of drinking water [34]. The pregnant women generally are victims of malnutrition and vitamin deficiency, and dietary supplements are not available. Most births take place at home and in the absence of a trained birth-attendant. Antenatal care is available to only about a quarter of pregnant women. In Kurram Agency, 91% of the families do not take supplemental iodine in their food, which is recommended for populations residing in high altitude areas. Iodine deficiency during pregnancy can lead to increased miscarriages and stillbirths, and other severe pregnancy and fetal outcomes. Likewise, the mortality rate for those <5 years old was 104 per 1,000 live births, while infant mortality rate was 86 per 1,000 births, which is the highest rate in Pakistan. These health issues have been further augmented by poor literacy, lack of proper health-safety measures, and malnutrition during pregnancy. Thus, this entire scenario may explain the high prevalence of sporadic, and not necessarily, genetic anomalies and neurological disorders, at least in part.

In conclusion, this epidemiological study in a war-affected area of Pakistan observed a high prevalence of neurological disorders among a cohort of 246 cases with CA. There was a preponderance of affected male individuals and sporadic cases. However, this study is

limited in that it did not attempt to show any direct impact of war-situations or other risk factors on the prevalence of CA, which may indeed exist. Further studies are warranted to observe the effect of environmental and nutritional factors, including war and insecurity on the incidence of CA, and to observe the molecular genetic bases of those anomalies. One of the objectives of this paper was to stimulate well-designed projects to examine such questions.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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