Burden of Congenital and Hereditary Anomalies in Hazara Population of Khyber Pakhtunkhwa, Pakistan

Anisa Bibi¹, Syeda Farwa Naqvi², Amman Syed³, Shah Zainab⁴, Khadija Sohail⁵, Sajid Malik⁶

ABSTRACT

Background and Objectives: In Pakistan, there is high incidence of congenital and hereditary anomalies (CA) which are a leading cause of infant mortality and morbidity. In order to elucidate the burden and biodemographic correlates of CA, this study was aimed to report the prevalence-pattern and phenotypic attributes of CA in the Hazara population of Khyber Pakhtunkhwa, Pakistan.

Methods: In a retrospective cross-sectional study, subjects/families with CA were recruited from district hospitals and community centers. Phenotypic and descriptive data were obtained; pedigrees were analyzed and parental and biodemographic attributes were recorded.

Results: A total of 1,189 independent subjects and/or families with CA were ascertained. The malformations were grouped into nine major and 95 minor categories. Neurological disorder had the highest representation (n=486; proportion=0.409; 95% CI=0.381-0.437), followed by limb defects (n=292; proportion=0.246, 95% CI=0.221-0.270), musculoskeletal defects, sensorineural/ear defects, blood disorders, eye/visual impairments, ectodermal anomalies, and congenital heart defects. In this cohort, sporadic cases were 65% and familial 35%. Parental consanguinity was significantly higher in isolated cases compared to syndromic, and in familial cases compared to sporadic. Further, speech apraxia and epilepsy were most common associations among the syndromic cases. The assessment of variables like demography, parental consanguinity, familial/sporadic nature, and pedigree structures showed conspicuous heterogeneity among the major and minor categories of CA.

Conclusions: The trend of CA and high incidence of sporadic cases observed in this cohort indicate that nongenetic factors may play a significant role in their etiology which could be minimized by improving the healthcare system.

KEYWORDS: Descriptive epidemiology, Genetic disorders, Birth defects, Neurological disorders, Limb anomalies.

doi: https://doi.org/10.12669/pjms.38.5.5486

How to cite this:
Bibi A, Naqvi SF, Syed A, Zainab S, Sohail K, Malik S. Burden of Congenital and Hereditary Anomalies in Hazara Population of Khyber Pakhtunkhwa, Pakistan. Pak J Med Sci. 2022;38(5):1278-1284. doi: https://doi.org/10.12669/pjms.38.5.5486

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Congenital and hereditary anomalies (CA) are the birth abnormalities of structure, function or metabolism that occur in developmental periods.¹ With the advancement in the control of infectious diseases, improvement of the healthcare system, hygiene and nutrition, CA have emerged as the main source of morbidity and mortality. The global prevalence of CA has been estimated to be 4%-5%.²,³ The burden of CA is very high in Pakistan due to various reasons including high rate of consanguineous unions, large sibships, low socio-
Anisa Bibi et al.

In Pakistan, the majority of the masses reside in rural areas where the healthcare infrastructure is inadequate.8 Hence, CA render extra burden on the low-resource healthcare system. Towards this end, a population-based study was carried out in order to elucidate the burden and prevalence-pattern of CA in the young and adult Hazara population of Pakistan.

METHODS

Study design and sampling area: A clinic-epidemiological study was carried out in Hazara division of Khyber-Pakhtunkhwa, Pakistan (www. pbs.gov.pk/). In a retrospective cross-sectional study design, the subjects and families with CA were recruited from District Headquarter Hospitals and special education centers during July 2018-Mar. 2021. Cases were also ascertained by visiting public places and community centers.

Ethical consideration: The study was approved by the Ethical Review Committee of Quaid-i-Azam University, Islamabad.(As-1070 July 8, 2015) All the data were acquired after informed consent according to Helsinki-II declaration. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement cross-sectional reporting guidelines.9

Classification of anomalies, statistical analyses: All the index cases were physically examined and diagnosed by the resident medical officers and/or specialized doctors. Pre-diagnosed cases registered at disability and rehabilitation centers were included. Participants belonging to the remote area were brought to the nearest district hospital for clinical examination. A detailed pedigree was constructed in each case. Only the index subject in each family was included in primary data analyses.

Anomalies with traumatic or infectious nature were excluded. Index cases were categorized on the basis of gender, familial/sporadic nature, and isolated/syndromic presentations. The following order was adopted for the classification of syndromic cases: neurological disorders, musculoskeletal defects, eye/visual impairments, sensorineural/ear anomalies, and limb defects. The definition of CA was based on a standard coding system of the International Classification of Diseases and Related Health Problems (ICD-10)6 and the corresponding definitions were identified in OMIM (www.omim.org) and Orphanet (www.orpha.net) databases.

Categorical variables were summarized; Chi-square and Fisher-exact test statistics were applied to check the significance of distribution and P < 0.05 was used as the cutoff for significance. For the CA, proportions and corresponding 95% confidence intervals (CI) were calculated.

RESULTS

Sample characteristics: A total of 1189 independent index cases were recruited, and the CA classified into nine major categories. Among the index cases, 678 (57%) were males (Table-I). The sporadic occurrence was more prominent compared to the familial nature (n=769 (65%) vs. n=420 (35%); respectively). Among all families, the total number of affected subjects was 2212 (1284 males, 928 females; P=0.0005).

In the gender-wise data, sensorineural/ear defects, blood disorders and congenital heart defects were more prevalent among the male subjects (65%, 64% and 62%, respectively), while eye/visual impairments, ectodermal anomalies, and ‘Others’ category were more prevalent among the index females (54%, 53% and 59%, respectively) (Table-I). Demographic attributes of the index cases are shown in Table-II.

Classification of congenital anomalies: The CA were resolved into nine major and at least 95 minor categories (Table-I, III). Among the major categories, neurological disorders were most frequent (n=486; 40.9%), followed by limb defects (24.6%), musculoskeletal defects (8.9%), sensorineural/ear defects (8.5%), blood disorders (6.3%), eye/visual impairments (3.3%), ectodermal anomalies (2.5%), congenital heart defects (2.2%), and Others (2.9%) (Table-I).

The neurological disorders were further grouped into 17 subcategories (Table-III). Among these, the most prevalent were intellectual disability (ID; n=176), cerebral palsy (148), epilepsy (n=41), autism/low IQ (n=25), Down syndrome (n=18), hydrocephaly (n=14), and microcephaly (n=14). Limb defects were resolved into 18 separate entities (detailed distribution given in Table-III).

Familial vs sporadic presentations and consanguinity: Analyses of pedigree structures revealed that there were 420 familial cases (35%) while remaining 769 (65%) had sporadic presentations (P<0.0001) (Table-I). The highest representation of familial cases was in ectodermal anomalies (77%), followed by eye/visual...
impairments (59%), while the lowest ratio was witnessed in neurological disorders (24%) and limb defects (35%).

The parental consanguinity in this cohort was estimated to be 66%; it ranged from 60% in limb defects to 81% in congenital heart defects (P=0.07). Consanguinity was significantly higher in the familial cases compared to sporadic (72% vs. 63%, respectively; P=0.004).

**DISCUSSION**

This is the first study reporting detailed clinical and descriptive epidemiological aspects of CA in the Hazara population of Pakistan. The prevalence-pattern of CA is useful implications in guiding resource allocation, management plans and therapeutic interventions.
Table-III: Major and minor categories of congenital/hereditary anomalies.

| Major/minor categories                          | Frequency | Proportion | 95% CI       | ICD-10  | OMIM   |
|------------------------------------------------|-----------|------------|--------------|---------|--------|
| **Neurological disorders**                      | 486       | 0.409      | 0.381-0.437  |         |        |
| Intellectual disability                        | 176       | 0.148      | 0.128-0.168  | F79     |        |
| Cerebral palsy                                 | 148       | 0.124      | 0.106-0.143  | G80.0   |        |
| Epilepsy                                       | 41        | 0.034      | 0.024-0.045  | G40     | 117100 |
| Autism/low IQ                                  | 25        | 0.021      | 0.013-0.029  | F84.0   |        |
| Down syndrome                                 | 18        | 0.015      | 0.008-0.022  | Q90     | 190685 |
| Hydrocephaly                                   | 14        | 0.012      | 0.006-0.018  | G91.9   | 236600 |
| Microcephaly                                   | 14        | 0.012      | 0.006-0.018  | Q02     | 251200 |
| Global developmental delay                     | 13        | 0.011      | 0.005-0.017  | Z13.42  | 618330 |
| Spina bifida                                   | 11        | 0.009      | 0.004-0.015  | Q05     | 182940 |
| Ataxia                                         | 7         | 0.006      | 0.002-0.010  | R27.0   | 160120 |
| Migraine                                       | 5         | 0.004      | 0.001-0.008  | G43     |        |
| Multiple sclerosis                             | 4         | 0.003      | 0.000-0.007  | G35     |        |
| Neuropathies                                   | 4         | 0.003      | 0.000-0.007  | G60.9   | 162400 |
| Macrocephaly                                   | 3         | 0.003      | 0.000-0.005  | Q75.3   | 153470 |
| Arnold Chiari malformation                     | 1         | 0.001      | -0.001-0.002 | Q07.0   | 207950 |
| Cystic encephalomalacia                        | 1         | 0.001      | -0.001-0.002 |        |        |
| Tremor                                         | 1         | 0.001      | -0.001-0.002 | R25.1   | 190300 |
| **Limb defects**                               | 292       | 0.246      | 0.221-0.270  |         |        |
| Talipes                                        | 141       | 0.119      | 0.100-0.137  | Q66.0   | 119800 |
| Polydactyly, postaxial                         | 34        | 0.029      | 0.019-0.038  | Q69     | 174200 |
| Polydactyly, preaxial                          | 31        | 0.026      | 0.017-0.035  | Q69.1   | 174400 |
| Transverse limb amputations                     | 23        | 0.019      | 0.012-0.027  | Y83.5   |        |
| Syndactyly                                     | 18        | 0.015      | 0.008-0.022  | Q70     | 609815 |
| Brachydactyly                                  | 10        | 0.008      | 0.003-0.014  | Q68.81  | 113000 |
| Clinodactyly                                   | 9         | 0.008      | 0.003-0.012  | Q74.0   | 148520 |
| Camptodactyly                                  | 7         | 0.006      | 0.002-0.010  | Q74.0   | 114200 |
| Leg length discrepancy                         | 4         | 0.003      | 0.000-0.007  | M21.7   |        |
| Constriction band syndrome                     | 3         | 0.003      | 0.000-0.005  | Q79.8   | 217100 |
| Thumb hypoplasia/aplasia                       | 3         | 0.003      | 0.000-0.005  |        | 188100 |
| Clubbing of digits                             | 2         | 0.002      | -0.001-0.004 | R68.3   | 119900 |
| Hallux valgus                                  | 2         | 0.002      | -0.001-0.004 | M20.1   |        |
| Fibular hypoplasia                             | 1         | 0.001      | -0.001-0.002 | Q73     |        |
| Macroductyly                                   | 1         | 0.001      | -0.001-0.002 | Q74.2   | 155500 |
| Radial hemimelia                               | 1         | 0.001      | -0.001-0.002 | Q73.8   |        |
| Symphalangism                                  | 1         | 0.001      | -0.001-0.002 | Q70.9   | 185800 |
| Trigger thumb                                  | 1         | 0.001      | -0.001-0.002 | M65.319 | 190410 |
| **Musculoskeletal defects**                    | 106       | 0.089      | 0.073-0.105  |         |        |
| Muscular dystrophy                             | 23        | 0.019      | 0.012-0.027  | G71.0   | 310200 |
| Hypotonia (limbs)/myopathies                   | 23        | 0.019      | 0.012-0.027  | P94.2   | 300868 |
| Dwarfisms                                      | 20        | 0.017      | 0.010-0.024  | E34.3   | 100800 |
| Congenital hip dysplasia                       | 11        | 0.009      | 0.004-0.015  | Q65.8   | 142700 |
| Scoliosis                                      | 6         | 0.005      | 0.001-0.009  | M41     | 181800 |
| Condition                                | Frequency | Confidence Interval | ICD Code | Code | Reference |
|------------------------------------------|-----------|---------------------|----------|------|-----------|
| Kyphoscoliosis                           | 4         | 0.003               | 0.000-0.007 | M40  | 610170    |
| Osteogenesis imperfecta                  | 4         | 0.003               | 0.000-0.007 | Q78.0| 166200    |
| Arthrogryposis                           | 2         | 0.002               | -0.001-0.004 | Q74.3| 108120    |
| Carpal fusion                            | 2         | 0.002               | -0.001-0.004 |     |           |
| Exostosis                                | 2         | 0.002               | -0.001-0.004 | Q78.6| 133700    |
| Klippel-Feil syndrome                    | 2         | 0.002               | -0.001-0.004 | Q76.1| 118100    |
| Pectus carinatum                         | 2         | 0.002               | -0.001-0.004 | Q67.7|           |
| DuPan syndrome                           | 1         | 0.001               | -0.001-0.002 |     | 228900    |
| Genu valgum                              | 1         | 0.001               | -0.001-0.002 | M21.06| 137370    |
| Muscular torticollis                     | 1         | 0.001               | -0.001-0.002 | M43.6| 189600    |
| Rheumatoid arthritis                     | 1         | 0.001               | -0.001-0.002 | M06  | 180300    |
| Rickets, vitamin-D resistant              | 1         | 0.001               | -0.001-0.002 | E83.3| 277440    |
| **Sensorineural/ear defects**            | **101**   | **0.085**           | **0.069-0.101** |     |           |
| Deaf and mute                             | 88        | 0.074               | 0.059-0.089 | H91.3| 304500    |
| Microtia/deformed pinna                   | 8         | 0.007               | 0.002-0.011 | Q17.2| 600674    |
| Speech apraxia                           | 3         | 0.003               | 0.000-0.005 | R47.9| 602081    |
| Deaf only                                | 1         | 0.001               | -0.001-0.002 |     |           |
| Mute only                                | 1         | 0.001               | -0.001-0.002 |     |           |
| **Blood disorders**                      | **75**    | **0.063**           | **0.049-0.077** |     |           |
| Thalassemia                              | 59        | 0.050               | 0.037-0.062 | D56  | 613985    |
| Hemophilia                               | 15        | 0.013               | 0.006-0.019 | D66  | 306700    |
| Fanconi anemia                           | 1         | 0.001               | -0.001-0.002 | D61.09| 227650    |
| **Eye/visual impairments**               | **39**    | **0.033**           | **0.023-0.043** |     |           |
| Blindness                                | 20        | 0.017               | 0.010-0.024 | H54  | 216900    |
| Squint/strabismus                        | 9         | 0.008               | 0.003-0.012 | H50.9| 185100    |
| Colour blindness                         | 3         | 0.003               | 0.000-0.005 | H53.5| 303800    |
| High myopia                              | 3         | 0.003               | 0.000-0.005 | H52.10|           |
| Night blindness                          | 3         | 0.003               | 0.000-0.005 | H53.60| 310500    |
| Anophthalmia                             | 1         | 0.001               | -0.001-0.002 | Q11.2| 251600    |
| **Ectodermal anomalies**                 | **30**    | **0.025**           | **0.016-0.034** |     |           |
| Atopic dermatitis/eczema                  | 8         | 0.007               | 0.002-0.011 | L20  | 603165    |
| Albinism, oculocutaneous                 | 5         | 0.004               | 0.001-0.008 | E70.3| 203100    |
| Alopecia totalis                         | 4         | 0.003               | 0.000-0.007 | L63.0| 208655    |
| Psoriasis                                | 3         | 0.003               | 0.000-0.005 | L40  | 177900    |
| Ectodermal dysplasia                     | 2         | 0.002               | -0.001-0.004 | Q82.4| 305100    |
| Hypotrichosis                            | 2         | 0.002               | -0.001-0.004 | Q84.0| 605389    |
| Ichthyosis                               | 2         | 0.002               | -0.001-0.004 | L85.0| 242300    |
| Alopecia areata                          | 1         | 0.001               | -0.001-0.002 | L63  | 104000    |
| Neurofibromatosis                        | 1         | 0.001               | -0.001-0.002 | Q85.0| 162200    |
| Onychodystrophy                          | 1         | 0.001               | -0.001-0.002 | L60.3| 161050    |
| Palmoplantar keratoderma                 | 1         | 0.001               | -0.001-0.002 | L40.3| 144200    |
| **Congenital heart defects**             | **26**    | **0.022**           | **0.014-0.030** |     |           |
| Ventricular septal defect                 | 12        | 0.010               | 0.004-0.016 | Q21.0| 614429    |
| Arterial septal defect                   | 6         | 0.005               | 0.001-0.009 | Q21.1| 108800    |
| Coronary artery disease                  | 5         | 0.004               | 0.001-0.008 | I125.10| 608901    |
| Atrioventricular canal defect             | 2         | 0.002               | -0.001-0.004 | Q21.2| 606215    |
CA related to the central nervous system (CNS) have been shown to be the most common types in many studies carried out internationally and locally.2,4,7 In our cohort, neurological disorders were observed to be the most prevalent (41%), followed by limb defects (25%) and musculoskeletal defects (9%). This pattern is also concordant with previous studies conducted in Pakistani populations of Lahore, Peshawar and Kurram Tribal Agency.4,10,11 In addition to a number of maternal, environmental and non-genetic factors, a likely reason for the high incidence of neurological disorders is that CNS requires an extended period of development and morphogenesis during embryonic development.

Among the neurological disorders, intellectual disabilities (ID) were most conspicuous in this cohort. Pakistan has been identified as one of the developing countries with the highest percentage of children with ID.12 Certain non-genetic factors like advanced maternal age at birth, minimal maternal education, low socioeconomic status, rural origin, less availability of healthcare system, poor antenatal care, maternal malnutrition and infections contribute to the increased rate of ID in developing countries including Pakistan.1,6

Limb defects were the second largest group of CA in the present cohort (25%). An epidemiological study on CA carried out in Sialkot, Pakistan, reported that limb defects were the most prevalent group (47%).5 In another study conducted in Kurram Agency of Northwest Pakistan, Zahra et al. reported that limb defects were the third most common types (21%), after neurological disorders (34%) and musculoskeletal defects (23%).11 Many limb defects are the source of disability, i.e., talipes, transverse limb amputations, leg length discrepancy, constrictive band syndrome, thumb hypoplasia/aplasia, fibular hypoplasia, radial hemimelia.

There was a high incidence of sporadic cases compared to the familial (65% vs. 35%). This observation is concordant with a recent epidemiological study carried out in Sialkot, Pakistan.5 In that study, the authors argued that a high preponderance of sporadic presentations among the limb and neurological disorders and a relatively reduced level of parental consanguinity may suggest a significant involvement of environmental factors in the etiology of these anomalies. Studies have shown that specific nongenetic factors may be involved in the etiology of certain types of CA. Brender and Weyer showed that there was a high risk of limb anomalies among the mothers who were exposed to agricultural compounds in water.13

The consanguinity rate was calculated to be 66% in our cohort and the highest rate of consanguinity evident in congenital heart defects (81%) and sensorineural/ear defects (77%). These observations are concordant with a study conducted by Zahra et al. who showed that the highest inbred unions were observed in children with congenital heart defects and deaf/mute cases.11 Furthermore, the familial cases had a significantly higher likelihood of parental consanguinity compared to the sporadic cases (P=0.004), which may suggest the key role of recessive genetic factors. In order to understand the more rational role of consanguinity in various
CA types, it would be worthwhile to estimate the background consanguinity in the population (see for instance Rittler et al.)\textsuperscript{14}.

**Limitation of the Study:** The current study has also several limitations. For instance, this study does not report the true prevalence or incidence rate of CA, and molecular diagnosis through mutation analyses or chromosomal investigations. Further, various physiological and metabolic disorders may remain unreported.

**CONCLUSION**

This study presents a comprehensive clinical and descriptive account of CA in the Hazara population of Pakistan. Neurological disorder, limb defects and musculoskeletal defects render the highest burden and comprised 74\% of the sample. The pattern of anomalies and the high incidence of sporadic cases may be indicative of nongenetic etiological factors. The burden of these anomalies can be minimized by improving health education, provision of antenatal and perinatal care, premarital counselling, genetic screening and molecular diagnosis of CA, and in general strengthening the healthcare system.

**Acknowledgements:** The volunteer participation of subjects/families is highly appreciated. We are indebted to the resident medical officers at various district hospitals of Hazara.

**Source of funding:** URF (QAU-2018-19).

**Conflict of interest:** None declared.

**REFERENCES**

1. WHO. World Health Organization. Congenital anomalies. 2020. https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies
2. Temtamy SA, Abdelmeguid N, Mazen I, Ismail SR, Kassem NS, Bassiony R. A genetic epidemiological study of malformations at birth in Egypt. East Mediterr Health J. 1998;4:252-259.
3. EUROCAT. 2020. European network of population-based registries for the epidemiological surveillance of congenital anomalies. https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en
4. Khan A, Zuhaid M, Fayaz M, Ali F, Khan A, Ullah R, et al. Frequency of Congenital Anomalies in Newborns and Its Relation to Maternal Health in a Tertiary Care Hospital in Peshawar, Pakistan. Int J Med Students. 2015;3(1):19-23. doi: 10.5195/ijms.2015.108
5. Bhatti NA, Mumtaz S, Malik S. Epidemiological study of congenital and hereditary anomalies in Sialkot District of Pakistan revealed a high incidence of limb and neurological disorders. Asian Biomed. 2019;13(2):49-60. doi: 10.1515/abm-2019-0010
6. WHO. World Health Organization. International Classification of Disease. ICD-10. 2010. http://apps.who.int/classifications/icd10/browse/2010/en
7. Gillani S, Kazmi NHS, Najeeb S, Hussain S, Raza A. Frequencies of congenital anomalies among newborns admitted in nursery of Ayub Teaching Hospital Abbottabad, Pakistan. J Ayub Med Coll Abbottabad. 2011;23:117-122.
8. Kumar S, Banu S. Comparison and Analysis of Health Care Delivery Systems: Pakistan versus Bangladesh. J Hosp Med Manage. 2017;3:1. doi: 10.4172/2471-9781.100020
9. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-349. doi: 10.1016/j.jclinepi.2007.11.008
10. Khan AA, Khattak TA, Shah SHA, Roshan E, Haq AU. Pattern of Congenital Anomalies in the Newborn. J Rawalpindi Med Coll. 2012;16(2):171-173.
11. Zahra Q, Shuaib M, Malik S. Epidemiology of congenital anomalies in the Kurram Tribal Agency, northwest Pakistan. Asian Biomed. 2017;10(6):375-385. doi: 10.5372/1905-7415.1006.529
12. Mirza I, Tareen A, Davidson LL, Rahman A. Community management of intellectual disabilities in Pakistan: A mixed methods study. J Intellect Disabil Res. 2009;53:559-570. doi: 10.1111/j.1365-2788.2009.01176.x
13. Brender JD, Weyer PJ. Agricultural compounds in water and birth defects. Curr Env Health Rep. 2016;3:144-152. doi: 10.1007/s40572-016-0085-0
14. Rittler M, Liascovich R, Lopez-Camejo J, Castilla EE. Parental consanguinity in specific types of congenital anomalies. Am J Med Genet. 2001;102(1):36-43. doi: 10.1002/1096-8628(20010722)102:1

**Authors Contribution:**

SM: conceived, designed and supervised the study; statistical analysis and manuscript writing.
AB, SFN, AS, SZ, KS: data collection and manuscript writing.
AB & SM: edited, reviewed and approved the manuscript.