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Study of congenital malformations in infants and children in Menoufia governorate, Egypt

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ABSTRACT

Congenital anomalies is one of the main causes of physical disabilities, stillbirths and neonatal deaths. The exact etiology of most congenital anomalies is unidentified but genetic and environmental causes are accused.

We aimed to study congenital anomalies regarding frequency, clinical pattern and associated risk factors.

A cross-sectional study was conducted on 100 infants and children with congenital anomalies attended to our pediatric genetic clinic at Menoufia University Hospital from October 2016 to October 2017. Detailed history taking, clinical examination and investigations including cytogenetic study were done.

Out of 100 cases, 51% have isolated anomalies and 49% have multiple anomalies, 14.2% had chromosomal abnormalities, 44.8% were diagnosed as genetic syndromes, while we did not reach the final diagnosis in 40.8% of cases. According to the ICD-10 classification of congenital anomalies musculoskeletal system anomalies were the most common in 48% of cases, followed by anomalies of the eye, ear, face and neck in 44% of cases. Anomalies of nervous system, circulatory system, genital organs, urinary system, chromosomal abnormalities, cleft lip and cleft palate occur in 26%, 22%, 18%, 12%, 7% and 6% of cases respectively.

Gastrointestinal anomalies in only 4% of cases taking into account that one case may have more than one affected system. According to the guidelines for case classification for the National Birth Defects Prevention Study, 2003, 51% had major anomalies, 18% had minor anomalies while 31% had both. Some cases had undergone immediate intervention e.g. meningomyelocele, encephalocele, omphalocele and gastroschisis. While other cases required later intervention e.g. hypospadius, cleft palate and cleft lip. Male gender, consanguineous marriage and lack of maternal folic acid supplementations were found in 54%, 43% and 59% of cases respectively, constituted the main risk factors.

Subjects and methods: proper physical examination, cytogenetic and molecular studies are important for the early intervention so prevention will be possible.

1. Introduction

Congenital anomaly has been defined according to the World Health Organization as any morphological, functional, biochemical or molecular defects that may develop in the embryo and fetus from conception until birth, whether detected at birth or later [1]. Approximately 3 million fetuses and infants are born each year with major malformations [2]. The prevalence of congenital and genetic disorders in infants and young children in Egypt ranges from 2.8% in urban areas to 8.4% in rural areas [3].

The causes of congenital anomalies are divided into single gene defects, chromosomal aberrations, multifactorial disorders, teratogenic factors and those of unknown etiology. Even with the great advances in genetics over the last decade, the etiology of more than 50% of malformations is still unknown [4]. Approximately 2–3% of neonates have a single major malformation, and 0.7% has multiple major defects [5].

Structural anomalies can be classified into anomalies that are due to abnormal tissue development (malformation and dysplasia) and others which arise after tissue development (deformation and disruption) [6]. The anomalies which affect an infant's life expectancy, health status, physical or social functioning may be described as "major" anomalies. In contrast, minor anomalies are

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those with little or no impact on health or short-term or long-term function [7].

Early and precise diagnosis of a child with multiple congenital anomalies is important for management, genetic counseling concerning etiology, recurrence risk, prenatal diagnosis, screening and recommendation for evaluation of other family members. Diagnosis of a child who presents with multiple congenital anomalies is still a complex issue.

2. Aim of the work

To study congenital anomalies as regards their frequency, clinical pattern, nature and the linked risk factors as well as to integrate an approach to reach a diagnosis of a dysmorphic child.

3. Patient and methods

The current study is a cross-sectional study which was conducted on 100 infants and children with congenital anomalies who attended our pediatric genetics clinic or admitted in the pediatric department-Menoufia university hospital from October 2016 to October 2017. Their ages ranged from 1 day to 12 years .

The cases were classified according to the guidelines for case classification for the national birth defects prevention study, 2003 [7] into cases with major anomalies and cases with minor anomalies with some cases having both. The anomalies also were classified according to the affected system according to the International Statistical Classification of Diseases and Related Health Problems, 10th version, for 2007 [8]. Also cases were classified into cases with single anomalies and cases with multiple anomalies which were further exposed to categorization according to their pattern trying to reach a diagnosis. Down syndrome was excluded to avoid high figures of chromosomal abnormalities.

After taking written informed consent of parents of affected children. The work has been carried out in accordance to the code of Ethics of the World Medical Association (Declaration of Helsinki For Experiments in Humans). Detailed history was taken regarding gender, gestational age, residence, maternal and paternal age at the time of conception, history of maternal illness or drug intake, maternal exposure to infections or teratogens, smoking (passive or active), folic acid supplementation, mode of delivery, history of previous abortions or stillbirths and obstetric complications. Three generation family pedigree was constructed for each case.

Physical characteristics were reported including the general appearance, body shape and size, craniofacial examination, neck examination as regards length, webbing and neck swelling and examination of extremities regarding symmetry, shortening of limbs and abnormalities of the fingers and toes. Anthropometric measures including internipple distance & internipple index were taken. Craniofacial anthropometric measures were taken including horizontal measures (head circumference, head length, head breadth, intercanthal distance, interpupillary distance, outer canthal distance, palpebral fissure length, philtrum width and commissural distance) and vertical measures (ear length, nose length, philtrum length, lower lip to chin). These measures were interpreted according to charts for craniofacial anthropometry [9,10]. Photographs were taken to document the dysmorphic features and the parents gave their approval for the publication of these photographic materials.

Investigations were asked including TORCH screening, abdomino-pelvic ultrasound and echocardiography for all cases and specific imaging studies as indicated for each case such as skeletal survey, C.T skull and MRI brain. Karyotyping was done for cases with multiple anomalies. Also Intelligent Quotient test was asked as indicated.

Cases with multiple anomalies were diagnosed by comparison with known cases indicated by the diagnostic search engine databases e.g. OMIM, Face2gene library and Genetic Home Reference. Results were analyzed by descriptive statistical techniques recording the number and percentage of the studied variables.

4. Results

We had studied 100 cases whose ages ranged from 1 day to 12 years. They were 54 males and 46 females. Demographic data revealed that regarding gestational age, 88% were full terms, 12% were preterms. As regards maternal age parameters, 71% of mothers were between 20 and 35 years, 23% were above 35 years and only 6% were below 20 years. History of consanguinity was

Table 1
Classification of the cases according to the provisional diagnosis.

Group I Single anomalies (n = 51)	Group II Multiple anomalies (n = 49)		
	Group IIa: Chromosomal anomalies (n = 7)	Group IIb: Syndromes, sequence, association or developmental field defect (n = 22)	Group IIc: Unknown diagnosis (n = 20)
Encephalocele (n = 1) Cystic hygroma (n = 1) Macroglossia (n = 1) Cleft palate (n = 4) Cleft palate and lip (n = 2) Cupped ear (n = 2) Preauricular tags(n = 2) Pectus excavatum (n = 1) Gastroschisis (n = 1) Phocomelia (n = 2), Polydactyly (n = 5) Syndactyly (n = 3) Polysyndactly (n = 3) Umbilical hernia (n = 5) Inguinal hernia (n = 6) Hypospadias (n = 4) Epispadias (n = 2) Undescended testicles (n = 3) Talipes equinovarus (n = 3)	46,XY,t(2:9)(q21:q31) 46,X,t(X:13)(p22.2:q12) 46,XY, add(17)(p13) 46,XY,del(4)(p16) 46,XX, del (18)(p11.2) 46,XX,deletion (18)(q) 45,XX,der(13:14)(q10:q10)	Seckel syndrome (n = 4) Treacher Collins syndrome (n = 1) Kartagener syndrome (n = 1) Caudal regression syndrome (n = 1) Apert syndrome (n = 2) Arnold chiari malformation (n = 1) Noonan syndrome (n = 1) Rubinstien Taybi syndrome (n = 1) Achondroplasia (n = 3) Osteogenesis imperfecta (n = 1) VACTERL association (n = 2) Meningomyelocele sequence (n = 2) Acrorenal polytopic developmental field (n = 2)	Cases who have anomalies whose combination cannot be categorized into syndrome, association, sequence or developmental field defects and karyotyping was normal

Table 2
Physical description of patients diagnosed as chromosomal abnormalities.

Chromosomal abnormality	Features
46,XY,t(2:9)(q21:q31)	Microcephaly, dysmorphic features (hypertolerism, deep seated eyes, low set ears), divarication of recti, right inguinal hernia, bilateral hydrocele, left talipes equinovalgus hypertonia & hyperreflexia.
46,X,t(X:13)(p22.2:q12)	Short stature, microcephaly, high forehead, synophyrus, bullous nose, depressed nasal bridge, pointed chin & hirsutism
46,XY, add(17)(p13)	Delayed motor & mental milestones, microcephaly, high forehead, squint, left sided ptosis, wide anteverted nares, thin upper lip, long philtrum, bilateral simian crease, VSD, umbilical hernia, scars of previously operated bilateral inguinal hernia & hypospadias, Fig. 1 (A).
46,XY,del(4)(p16) (Wolf Hirshhorn syndrome)	Delayed motor & mental milestones, hypotonia, microcephaly, flat facies, high forehead, arched eyebrows with sparse hair on their medial parts, hypertolerism, broad nasal bridge, short philtrum, carp shaped mouth, microretrognathia, large ears, preauricular pits, Fallot tetralogy, hypospadias & hypotonia, Fig. 1 (B)
46,XX, del (18)(p11.2)	Delayed motor & mental milestones, left sided ptosis, bilateral medial epicanthic folds, malformed left ear, low set ears, broad nasal tip, and mild retrognathia & decreased Growth hormone level, Fig. 1(C)
46,XX,deletion (18)(q)	Delayed motor & mental milestones, deep setted eyes, carp shaped mouth, notched helical fold of right ear, ASD, hypotonia, convulsion, CNS demyelination on MRI brain.
45,XX,der(13:14) (q10: q10)	Hypotonia, upward slanting of eyes, ear tag on right side, depressed nasal bridge.

positive in 43% of couples. As regards maternal and obstetric history, 56% of neonates were delivered by caesarean section while 44% by the vaginal route. Besides, 10% of the mothers have chronic diseases in the form of diabetes mellitus, hypothyroidism. Folic acid supplementation was not received by 41% of the mothers.

According to the International Statistical Classification of Diseases and Related Health Problems, 10th version, for 2007, 48% of cases had musculoskeletal anomalies followed by 44% had anomalies of the eye, ear, face and neck, followed by nervous system anomalies in 26%, circulatory system anomalies in 22%, genital organs anomalies in 18%, urinary system anomalies in 12%, chromosomal abnormalities in 7%, cleft lip and cleft palate in 6% and the gastrointestinal anomalies in only 4% of cases.

According to the guidelines for case classification for the national birth defects prevention study, 2003, 51% of the cases had major anomalies, 18% had minor anomalies while 31% had both. According to their provisional diagnosis cases were classified where 51% have single anomalies, 49% have multiple anomalies, of which, 7 cases about 14.2% had chromosomal abnormalities, 22 cases about 44.8% were diagnosed as known genetic syndromes, associations, sequences and developmental field defects, while we did not reach the final diagnosis in 20 cases about 40.8% (Table 1). Physical description of diagnosed cases was summarized in (Tables 2 and 3). Photographs of some of these cases are shown in (Figs. 1–3).

5. Discussion

This study was carried out on 100 infants and children who have congenital anomalies. We found that the rate of CMs outnumbered in males 54% compared to females 46% which was consistent with the results of other studies [1]. On the other hand Abdi-Rad

Table 3
Physical description of cases diagnosed as syndromes, sequences, association and developmental field defects.

Diagnosis	Features
Seckel syndrome (n = 4) (1 female & 3 males)	All four cases have proportionate dwarfism, intrauterine growth retardation, mental retardation, microcephaly with bird – headed profile (large eyes, beaked nose, receding chin, micrognathia). History of consanguineous marriage suggests the autosomal recessive inheritance of Seckel syndrome. Also case (1) had in clinodactyly, case (2) had dolichocephaly and case (4) had bilateral simian crease, talipes equinus, posteriorly rotated ears and pachygyri. All of these features are reported in seckel syndrome.
Treacher Collins syndrome (n = 1)	Female child with defective hearing, microtia, cupped ears with thickened helical fold, downward slanting of the eyes; bilaterally notched lateral portion of the lower eyelids, mild retrognathia & clinodactly. Family history of three similar conditions was present suggesting the autosomal dominant inheritance of the syndrome.
Kartagner syndrome (n = 1)	Male child with dextrocardia, situs inversus totalis, recurrent sinusitis, bronchiectatic changes of both lungs. Paternal consanguinity is consistent with the autosomal recessive inheritance of primary ciliary dyskinesia.
Caudal regression syndrome (n = 1)	Female child with short stature, reduced sacral area with wasted gluti & muscles of the lower limbs and MRI picture of sacral agenesis. Also has bilateral hydronephrosis and grade 3 nephropathy and neurogenic bladder. History of maternal insulin dependent diabetes mellitus.
Apert syndrome (n = 2)	Female child with microcephaly, brachecephaly, high forehead, bilateral coronal synostosis, depressed nasal bridge, complete complex syndactly between fingers of both hands and complete complex syndactly between toes of both feet.
Arnold chiari malformation (n = 1)	Female child with Hydrocephalus, scar of excised meningomyelocele, neurogenic bladder, left talipes equinovalgus & right talipes calcaneovalgus and dysmorphic features. History of lack of folic acid and vitamin B12 during pregnancy was present.
Noonan syndrome (n = 1)	Male child with delayed motor and mental milestones, Short stature, hypertolerism, bilateral medial epicanthic folds, thickened helix, thin upper lip, deeply grooved philtrum, retrognathia, webbed neck, eczematous skin lesions, cryptorchidism and hypertrophic cacdiomyopathy.
Rubinstien Taybi syndrome (n = 1)	Female child with delayed motor & mental milestones, high forehead, frontal bossing, and broad nasal bridge, convex nose profile with the nasal septum extending below the nasal alae, mild micrognathia, bilateral broad angulated thumbs, and bilateral broad angulated big toes. Ultrasound picture of developmental dysplasia of the hips. MRI brain showed agenesis of corpus callosum and previously operated congenital glaucoma & cataract.
Meningomyelocele sequence (n = 2)	They have meningomyelocele, talipes equinovarus.
VACTERL association (n = 2) (2 males)	Both cases have meningomyelocele, very short forearm (absent radius), short broad fingers of the right hand, partially absent thumb bones, ulnar deviation of the two hands, bilateral talipes equinovarus. One case also had ventricular septal defect and the other case had imperforate anus.
Achondroplasia (n = 2)	Disproportionate rhizomelic short stature, macrocephaly, small thoracic cage, lumber lordosis, brachydactyly, prominent forehead &depressed nasal bridge.
Osteogenesis imperfect (n = 1)	Soft skull bone, wide fontanelles, brachecephaly, Joint hypermobility, dislocation of shoulder joint.
Acrorenal polytopic developmental field (n = 2)	One case has absent thumb & hypospadius. left vesicoureteric reflux, left sided hydronephrosis. The other case has unilateral renal hypoplasia & Syndactyly.

Fig. 1. Physical characteristics of three cases with chromosomal abnormalities: (A) Male child with 46XY, add 17P13; (B) Male child diagnosed as a Wolf Hirshhorn syndrome (46XY,del(4)(p16); (C) Female child with 46 xx, del (18)(p11.2).

et al. reported a higher occurrences of congenital anomalies was found among women. In females 1.99%, in males 1.68% but with non-statistically significant difference [11]. Another study showed that there is no significant association between gender of the babies and the development of congenital anomalies [12].

In the current study the full terms represented 88%, while the preterm ones represented 12%. Other studies showed a high occurrence of birth defects among premature infants and /or those of low birth weight [13,14]. Our finding could be explained that the age of the cases ranged between 1 day to 12 years not limited to newborns and the full terms are naturally selected.

Maternal age is an important parameter in the birth of a child with congenital malformation [15]. In our study, it was found that a high occurrence of congenital abnormality was found among women who are between 20 and 35 years of age about 71%. Our study agreed with other literature which noted that high pregnancy rates among mothers in this age range could account for increased frequency of congenital anomalies [16]. Other studies reported an incidence of 6.1% in mothers with age >30 years and the incidence of 8.7% in older mothers [17,18].

Consanguinity is considered a controversial association with CMs. In our study history of consanguinity was positive in 43% of couples. This is consistent with an Egyptian study, which reported that consanguinity was significantly associated with the presence of congenital anomalies 3.67% compared with control populations 1.15% [19].

About the mode of delivery, CS dominance 56% was noted among our patients. A significantly higher frequency of congenital anomalies in neonates delivered by CS than the control population 54.4% versus 29.7% was also documented [20]. This could be

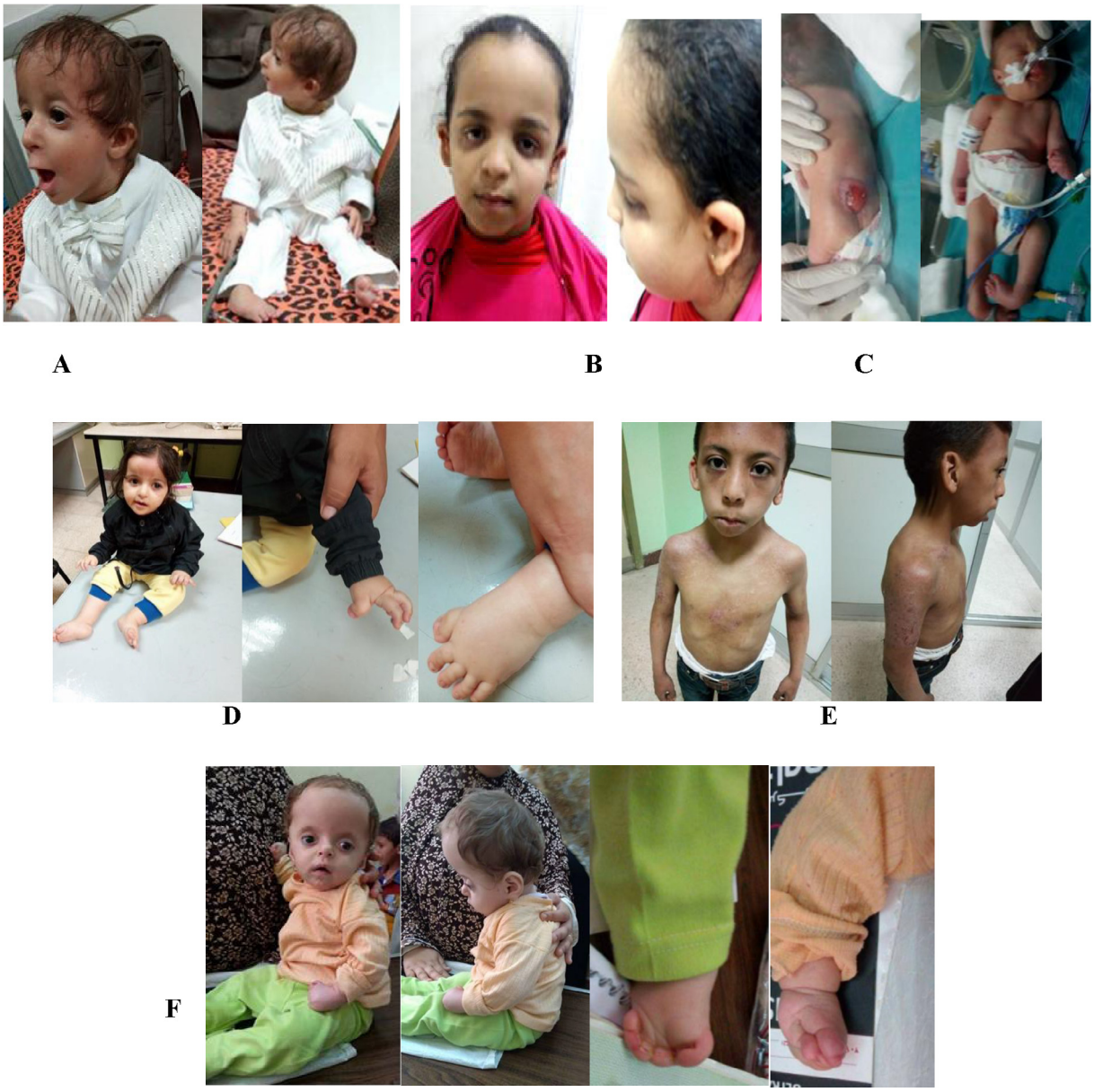

Fig. 2. Some of cases provisionally diagnosed as syndromes and associations: (A) Seckel syndrome; (B) Treacher Collin syndrome; (C) VACTREL Association; (D) Rubinstein-Taybi syndrome; (E) Noonan syndrome; (F) Apert syndrome.

contributed to that the rate of cesarean section has been increased in the last years [21]. The other probable explanation could be its fetal indication due to prenatal diagnosis of CM [22]. However, another study demonstrated no association between the frequency of congenital anomalies and the route of delivery [2].

Folic acid supplementation has been proven to decrease or minimize specific birth defects [23]. In our study, we found that 41% of the mothers of our cases were receiving folic acid supplementation during pregnancy compared to the higher percentage 59% that was not. This goes with a study done by Shawky and Sadik which reported that only 27.5% of mothers of patients with CMs received folic acid or multivitamin which is significantly lower than that in the controls [2].

As regards the affected systems, it was found that musculoskeletal anomalies were the most common followed by craniofacial anomalies and nervous system anomalies. This is in accordance with a study which showed that the most common system involved was musculoskeletal system 33.2% [24]. Another study recorded higher incidence of CNS 30.2% malformations followed by GIT 15.2% and musculoskeletal system 10.4% [25]. These variations between different studies could be explained by the effect of different racial, ethnic and social factors in various parts of the world or different geographical, nutritional, socioeconomic factors and variations in the criteria of diagnosis and the basis of classification [26]. Gastrointestinal malformation was found to be the most common single system abnormality detected by Sawardekar, although in his study orofacial clefts (cleft lip and/or palate) were included in the GIT malformations [27].

According to the guidelines for case classification for the national birth defects prevention study, 2003, 51% of the cases had major anomalies, 18% had minor anomalies while 31% had both. The importance of this classification is to predict the prognosis, determine intervention and its urgency and expect the long term functioning of the child.

The causes of congenital malformations are divided into four broad categories, genetics, environmental, multifactorial and

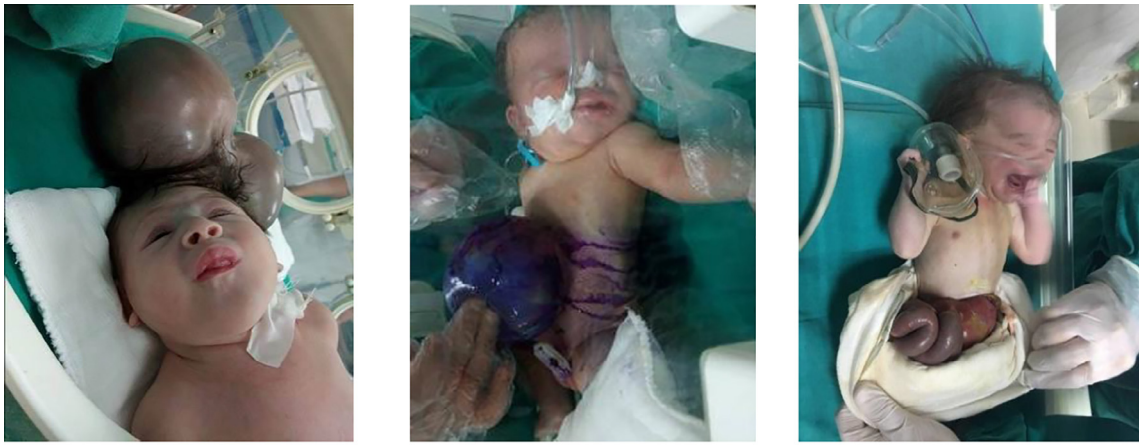

Fig. 3. Three of cases with major anomalies: (A) Encephalocele; (B) Congenital omphalocele; (C) Gastroschisis.

unknown. The genetic cause is considered to be responsible for as many as 10–30% of all birth defects, environmental factors in 5–10%, multifactorial inheritance in 20–35% and unknown causes were responsible for 30–45% of cases [28]. Our study showed that single anomalies represented 51% whereas multiple anomalies constituted 49% of which 14.2% have chromosomal abnormalities, 32.6% have clinically diagnosed genetic syndromes, 12.2% were categorized as associations, sequences & developmental field defects and 40.8% cannot be diagnosed. A study done in Egypt on the etiology of multiple CMs, multiple anomalies constituted 21.4%, genetic syndromes 31% and 47.6% were due to unknown causes [29].

With the increasing identification of the genetic causation of disease, reaching a provisional clinical diagnosis allows a more targeted search for a genetic etiology. Making a diagnosis allows early and proper intervention for the disease or its complications, allows the parents to search for and join a 'support group' and interact with other parents with children having the same or similar problems and also allows providing genetic counseling [30].

Genetic counseling is a communication process of providing individuals and families with information on the nature, inheritance and implications of genetic disorders, including recurrence risks, to help them make informed medical and personal decisions [31]. In this study, the recurrence risk was demonstrated. For cases with structural chromosomal aberrations (visible deletion and unbalanced translocation), parental karyotype was ordered which was normal so the recurrence risk was demonstrated to be low. For cases with autosomal dominant disorders as Achondroplasia, Apert syndrome and Treacher Collin syndrome and Noonan syndrome, it seemed that they mostly are fresh mutations because the parents were normal and that the risk of the single mutated gene to be passed to a given offspring was 50%, yet the risk of severe disease was less than 50% because of variation in expression. For cases with autosomal recessive disorders as Seckel syndrome and Kartagner syndrome, it was demonstrated that the likelihood of recurrence increases with the consanguineous marriage. For some cases which are mostly of multifactorial inheritance the recurrence risk was nearly similar to that found by Jones et al. who showed that recurrence risk for cleft lip with or without cleft palate is 4–5%, for cleft palate alone is 2–6% and for meningomyelocele is 3–5% [32].

6. Conclusion

CMs are not uncommon in our community with the musculoskeletal anomalies were the most common in our study. Male gender, positive consanguinity, lack of folic acid supplementation were the associated risk factors. Proper physical examination, special charts for craniofacial anthropometry, knowledge about the incidence and pattern of congenital a anomalies, prenatal diagnosis and family counseling are important .lines to plan preventive strategies at different levels by healthcare providers.

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