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Congenital Malformations: Report of 5 Rare Cases Seen in 20 Years (1994-2014) in Cameroon and Review of Literature

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Case Report

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ABSTRACT

We report 5 rare congenital malformations found in 20 years of practice (1994-2014) in our service amongst 3 females and 2 males. Multisystem malformations involve more than one system and are rare. We found a case of amelia (lower limb) associated with gastroschisis, congenital bilateral polycystic kidneys, unilateral uterine adnexal agenesis fortuitously discovered in an adult and a congenital huge haemangioma of the nasal tip and dorsum giving a 'clown nose deformity'. Most spectacularly, we describe a foetus born with extra oral location of all organs of the gastrointestinal tract enclosed in a thin transparent membrane. To the best of our knowledge this condition has not been described before and so we decided to call it 'entero-oro exogenesis' and ascribe to it the eponym 'Enow Orock syndrome' in reference to the pathologist who first described it. In all our cases, no etiological factor could be attributed to any of the conditions due largely to lack of collaboration from the affected families and logistic challenges. The only recurring risk factor that was common to all our cases was a low socioeconomic status of parents of the patients. Malformations are not rare in our community. The absence of a congenital malformation registry makes data on the disease difficult to obtain in Cameroon. We recommend that a national registry for the condition be created and public education intensified on birth defects in our community.

INTRODUCTION

A congenital malformation (CM) is a congenital structural defect that often occurs in the first trimester. Although significant progress has been made in identifying the etiology of some birth defects, approximately 65% have no known or identifiable cause [1-3]. For 20-25% of anomalies there seems to be a "multifactorial" cause, involving a complex interaction of multiple minor genetic anomalies with environmental risk factors. Another 10-13% of anomalies have a purely environmental cause (e.g. infections, illness, or drug abuse in the mother). Only 12-25% of anomalies have a purely genetic cause. Of these, the majority are chromosomal anomalies [4]. CMs are of random occurrence regardless of maternal living conditions and a low recurrence risk for future children.

It is estimated that 10% of all birth defects are caused by prenatal exposure to a teratogenic agent [1]. These exposures include, but are not limited to, medication or drug exposures, maternal infections and diseases, environmental and occupational exposures. Paternal smoking use has also been linked to an increased risk of birth defects and childhood cancer for the offspring, as it is suspected that paternal germ line undergoes oxidative damage due to cigarette use [5,6]. Genetic causes of congenital anomalies include inheritance of abnormal genes from the mother or the father, as well as new mutations in one of the germ cells that gave rise to the fetus. Male germ cells mutate at a much faster rate than female germ cells, and as the father ages, the DNA of the germ cells mutates quickly [5,7]. If an egg is fertilized with sperm that has damaged DNA, there is a possibility that the fetus could develop abnormally [7,8]. With a global increasing life expectancy, exposure to man-made and natural environmental and life style hazards in a rapidly changing world, it is predictable that many yet-to-be described CMs shall see the light of day in future.

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CASE REPORTS

Case 1: Multi-system congenital malformations- gastroschisis associated with amelia

NS is a 29 years old single student, non-smoker with an uneventful first pregnancy seen at 16 weeks. She is a 5th child in a family of 7 comprising 4 boys and 3 girls. Her family and social history is not contributory. She had been on "Nolevo" oral pill for several years. The author of the pregnancy is a 34 years old commercial agent, 1st child in a family of 6 comprising 2 boys and 4 girls. There was no family history of a congenital malformation in both families. The mother lived in a suburban environment.

An ultrasound done at 16 weeks noted the absence of a lower limb and evisceration of abdominal organs. A decision to abort the pregnancy for severe malformation(s) was reached with consent of the mother. A male foetus of 35 cm CR length was found in the abortus. The abdominal wall was absent and entire gut was found out of the body cavity. There was a total absence of the left lower limb. A plain X-ray confirmed a total absence of the left lower limb. All other organs were macroscopically normal **(Figures 1-3).**

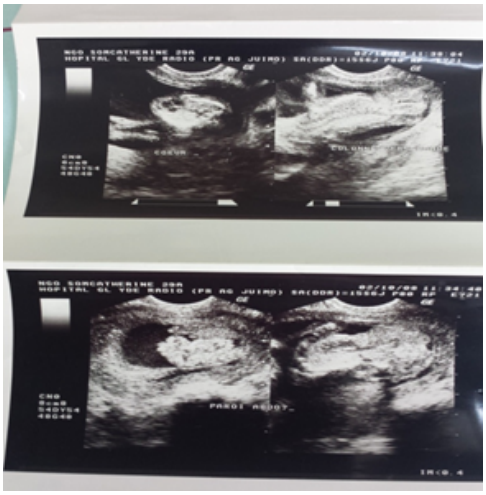

Figure 1. Ultrasound showing (lower limb) amelia and gastroschisis in a 16 weeks old foetus.

Figure 2. Macroscopic image of gastroschisis and amelia in a 16 weeks old foetus.

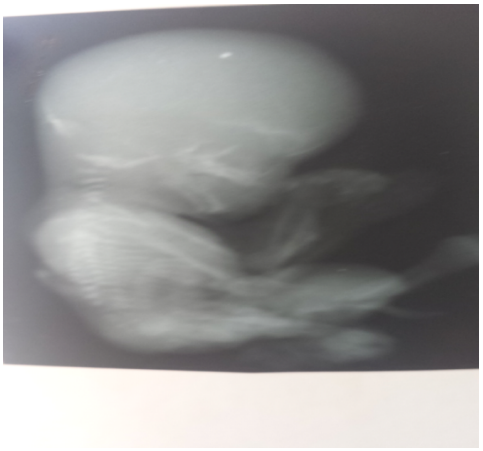

Figure 3. X-ray confirmation of lower limb amelia.

Case 2: Congenital bilateral polycystic "sponge" kidneys

A full-term female foetus was delivered after an oligohydramniotic pregnancy to a 39 years old civil servant. Fifth child of a family of 5 with no relevant family or social history. The child died 1 week after delivery from uraemia. Autopsy revealed bilateral sponge kidneys with total loss of cortico-medullary renal parenchyma replaced by cystic cavities **(Figure 4).**

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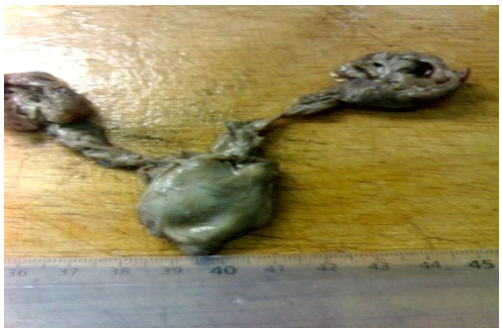

Figure 4. En bloc' dissection of the kidneys, ureters and bladder with cross-section of left kidney showing bilateral "sponge" kidneys.

Case 3: Congenital total agenesis of right uterine adnexa

A 54 years old female executive G5P4A1 presented with metrorrhagia of long duration and was assessed to have a uterine leiomyoma. She had never had any previous surgery or obstetric complications. She was booked for a total abdominal hysterectomy. Incidentally the surgeon found a total agenesis of the right uterine adnexa. This specimen at pathology confirmed the malformation alongside a serous cyst of the left ovary and an intramural leiomyoma associated with adenomyosis of the uterine corpus **(Figures 5 and 6).**

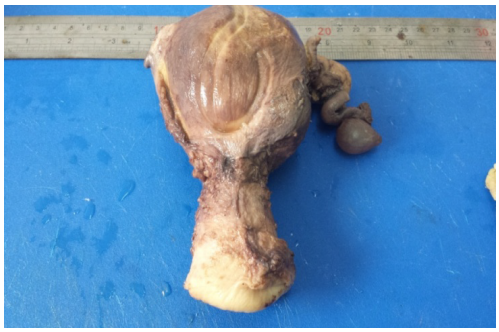

Figure 5. Total right adnexal agenesis.

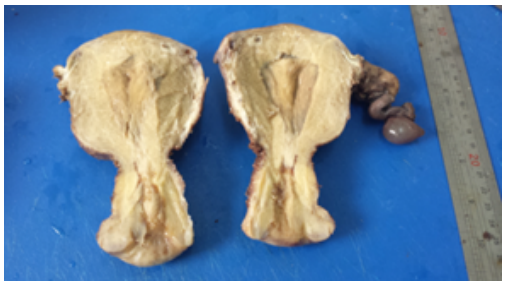

Figure 6. Right adnexal agenesis.

Case 4: 'Entero-Oro-Exogenesis'- 'Enow Orock Syndrome'

A 36 year old G3P1A2 was admitted into labour for a full term uneventful pregnancy. A naive echographist had diagnosed her pregnancy as multiple and normal. She had obstructed labour and was delivered by Caeserian section of a single full term female child. A congenital malformation that consisted of oral extrusion of the entire alimentary system including the gut, liver and pancreas was noted. These organs were macroscopically mature and all bound by a thin transparent membrane. The CR length was 45cm and the limbs were exaggeratedly long with obvious arachnodactylly. Genetic investigations, radiology and a foetopsy were proposed but the family categorically refused **(Figure 7).**

Figure 7. "Entero oro-exogenesis" with Marfanoid features including exaggerated height, and arachnodactylly –"Enow Orock syndrome."

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Case 5: Congenital nasal haemangioma giving a "clown nose" deformity

A 2 months old male infant was referred to our service for biopsy and histopathology of a congenital nasal tumor. The patient was second child in a family of 2. The senior sister was alive, normal and well. The unemployed mother had been administered all indicated antenatal immunizations and had no illness during pregnancy. She is married and a non-smoker. The father is a businessman. They lived in a rural part of the city. Examination showed a well-developed male infant with a tumor occupying the tip and dorsum of the nose and measuring about 3cm maximal diameter. The mass was cystic and non tender and non pulsatile. A biopsy and examination showed the tumour to be a haemangioma. The patient was referred to the ENT surgeon for rhinoplasty and lost to follow up **(Figure 8).**

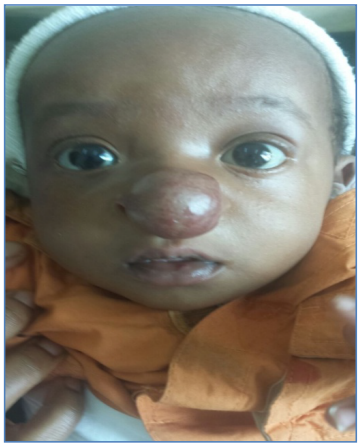

Figure 8. "Clown nose" deformity due to a congenital nasal dorsal haemangioma.

DISCUSSION

Congenital malformations are the leading cause of infant mortality in the United States [9]. They are the fifth leading cause of years of potential life lost and a major cause of morbidity and mortality throughout childhood [10]. Twenty percent of infant deaths are attributed to congenital malformations, a percentage that has increased over time. Approximately 25% of paediatric hospital admissions and about one-third of the total number of paediatric hospital days are for congenital malformations of various types [11]. Not much is known about the causes of congenital malformations. Twenty percent may be due to a combination of heredity and other factors; 7.5% may be due to single gene mutations; 6% to chromosome abnormalities; and 5% to maternal illnesses, such as diabetes, infections or anticonvulsant drugs [12]. Birth defects are reported to be more common in males, with a male: female sex ratio ranging between 1.22-1.29:1 [13,14]. We found an inverse ratio of 60% females against 40% males in this study.

Birth defects are present in about 3% of newborns. Congenital anomalies resulted in about 632,000 deaths per year in 2013 down from 751,000 in 1990 [15]. According to the CDC, most birth defects are believed to be caused by a complex mix of factors including genetics, environment, and behaviors, though many birth defects have no known cause [16].

Drinking water is often a vessel through which harmful toxins travel. Studies have shown that heavy metals, elements, nitrates, nitrites, fluoride can be carried through water and cause congenital disorders. A case-control study in rural Australia that was conducted following frequent reports of prenatal mortality and congenital malformations found that those who drank the nitrate-infected groundwater, as opposed to rain water, ran the risk of giving birth to children with central nervous system disorders, musculoskeletal defects, and cardiac defects [17].

A study on twenty-one European hazardous waste sites showed that persons living within three kilometers had an increased risk of giving birth to infants with birth defects and that as distance from the land increased, the risk decreased. These birth defects included neural tube defects, malformations of the cardiac septa, anomalies of arteries and veins, and chromosomal anomalies [18]. Concerning communities that live near landfill sites, a vast majority of them are poor communities. A study conducted on a Welsh community also showed an increase incidence of gastroschisis amongst these inhabitants. Our case with musculo-skeletal defects was an association of amelia involving the left lower limb and gastroschisis **(Figures 1-3).**

Very few studies have investigated the links between paternal alcohol use and offspring health [19]. The prevalence of children affected by alcohol use of parents is estimated at 1 percent in the United States as well as in Canada [20].

Currently rubella is known to cause abnormalities of the eye, internal ear, heart, and sometimes the teeth. More specifically, fetal exposure to rubella during week five to ten of development, particularly the sixth week, can cause cataracts and microphthalmia. If the mother is infected with rubella during the ninth week, a crucial week for internal ear development, there can be destruction of the organ of Corti, causing deafness. In the heart the ductus arteriosus can remain after birth, leading to hypertension. Rubella can also lead to atrial and ventricular septal defects in the heart.

If exposed to rubella in the second trimester, the foetus can develop central nervous system malformations. However,

because infections of rubella may remain undetected, misdiagnosed, or unrecognized in the mother, and/or some abnormalities are not evident until later in the child's life. Precise incidences of birth defects due to rubella are not entirely known. The current introduction of rubella vaccination in the National Expanded Program on Immunization in Cameroon is a welcome relief.

Other infectious agents that can cause CMs include cytomegalovirus, herpes simplex virus, hyperthermia, toxoplasmosis, and syphilis. Mother exposure to cytomegalovirus can cause microcephally, cerebral calcifications, blindness, chorioretinitis, hepatosplenomegaly, and meningoencephalitis in fetuses [21]. However, cytomegalovirus is often fatal in the embryo. A lack of folic acid and/or vitamin B, in the diet of a mother can cause cellular neural tube deformities that result in spina bifida.

Congenital disorders such as a neural tube deformity can be prevented by 72% if the mother consumes 4 milligrams of folic acid before the conception and after 12 weeks of pregnancy [22]. Folic acid and/or vitamin B_{12}, aid the development of the foetal nervous system. The most typical disorder induced by thalidomide is reductional deformities of the long bones of the extremities (phocomelia), otherwise a rare deformity.

A low socioeconomic status in a deprived neighborhood may include exposure to "environmental stressors and risk factors" [23]. Socioeconomic inequalities are commonly measured by various scores which consider unemployment, overcrowding, single parents, under-fives, elderly living alone, ethnicity, low social class and residential mobility [24]. In Vos' meta-analysis these indices were used to view the effect of low socioeconomic status neighborhoods on maternal health from 1985 to 2008. Vos concludes that a correlation exists between prenatal adversities and deprived neighborhoods [24].

Other studies have shown that low status is closely associated with the development of the foetus in utero and growth retardation [25]. Studies also suggest that children born in low status families are likely to be born prematurely, at low birth weight, with asphyxia, a birth defect, a disability, foetal alcohol syndrome, or AIDS [25]. Bradley and Corwyn also suggest that congenital disorders arise from the mother's lack of nutrition, a poor lifestyle, maternal substance abuse and living in a neighborhood that contains hazards affecting fetal development (toxic waste dumps) [25]. All our cases were off springs of low socioeconomic parents and the CMs were found at birth except in the case of adnexal agenesis **(Figures 1-8).**

Animal studies have shown that X-ray irradiation of male mice resulted in birth defects of the offspring [26]. The effects of paternal age on offspring are not yet well understood and are studied far less extensively than the effects of maternal age [27]. Fathers contribute proportionally more DNA mutations to their offspring via their germ cells than the mother, with the paternal age governing how many mutations are passed on. This is because, as humans age, male germ cells acquire mutations at a much faster rate than female germ cells [28,29].

Around a 5% increase in the incidence of ventricular septal defects, atrial septal defects, and patent ductus arteriosus in offspring has been found to be correlated with advanced paternal age. Advanced paternal age has also been linked to increased risk of achondroplasia and Apert syndrome. Similarly, offspring born to fathers under the age of 20 show increased risk of being affected by patent ductus arteriosus, ventricular septal defects, and the tetralogy of Fallot. It is hypothesized that this may be due to environmental exposures or lifestyle factors [27].

Research has found that there is a correlation between advanced paternal age and risk of birth defects such as limb anomalies, syndromes involving multiple systems, and Down's syndrome [28,30]. Many studies have found that the frequency of occurrence of certain congenital malformations depends on the sex of the child [31-35]. Rajewski and Sherman have analyzed the frequency of congenital anomalies in relation to the system of the organism [36]. Prevalence of men was recorded for the anomalies of phylogenetically younger organs and systems [36]. Defects with male predominance include congenital anomalies of the genitourinary system which occur with a male: female ratio of 2.7:1. The case we report involved a female **(Figure 4).** In a study in the United States 2004-2006, gastroschisis was found to occur in 1 in 2,229 live births per year with an estimated incidence of 187 [37]. Also, reduction deformities involving the lower limb occurred in 1 in 5,949 live births per year with an incidence of 1871 [37].

CONCLUSION

There is no birth defect registry in Cameroon and data on such defects is largely inexistent. However congenital anomalies are seen but often unreported from various obstetric and paediatric services across the country. In the case where such cases are reported, the family is usually uncollaborative and detail investigations to identify potential risk factors are unavailable. Knowledge on CMs and their risk factors in our environment is essential for prevention, early detection and long and short term management. It is in order to raise awareness that we decided to publish these rare congenital defects that we found in the course of 20 years of practice in our community.

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