Modern Applied Science; Vol. 13, No. 2; 2019
ISSN 1913-1844 E-ISSN 1913-1852
Published by Canadian Center of Science and Education

Dysencephalia Splanchnocystica, AKA Meckel–Gruber syndrome: A Systematic Review and the First Case Report from Iraq

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Received: December 8, 2018 Accepted: January 2, 2019 Online Published: January 14, 2019

doi: 10.5539/mas.v13n2p149 URL: https://doi.org/10.5539/mas.v13n2p149

Abstract

Background

Meckel-Gruber syndrome is categorised under the broad "umbrella" of syndromic ciliopathies. There is a shortage of epidemiological studies surveying the region of the Middle East and Arabic countries.

Materials and methods

The review of the literature was conducted systematically, from the 1st to the 9th of June 2018, across medical and paramedical electronic databases including PubMed-NCBI, the Cochrane Library, and Elsevier database via predefined Medical Subject Headings (MeSH) terms. The words used included all possible combinations of synonyms for Meckel syndrome, Meckel-Gruber syndrome, Gruber syndrome, Dysencephalia Splanchnocystica, ciliopathies, and syndromic ciliopathies.

Results

The total number of hits for all databases was 2089963 distributed as 2085668 (NCBI-PubMed), 1052 (The Cochrane Library), and 3243 (Elsevier). The most informative combination of keywords was [(Ciliopathies AND "Meckel syndrome type-1"]. The total number of reference material was restricted to twenty-six. The level-of-evidence of our study is level-2b, by the categorisation scheme adopted by the Oxford Centre for Evidence-based Medicine. Our case report represents the first documented case in literature from Iraq. The diagnosis was based on the history of consanguinity of the parents, prior history of induced abortion of a malformed male fetus, and the diagnostic clinical triad postnatally of occipital encephalocele, post-axial polydactyly, and polycystic kidneys manifested as bilateral abdominal distension primarily affecting the loin.

Conclusion

Future cases from Iraq should be investigated, via ecological and aggregate analytics, in correlation with chemical and radiological exposure following the American invasion of Iraq.

Keywords: Meckel Syndrome type 1, Dysencephalia Splanchnocystica, Ciliary Motility Disorders, Ciliopathies, Arabs, Iraq

1. Introduction

Ciliopathies including *Meckel-Gruber syndrome* (MGS) impose substantial consequences affecting the society and the economy. In the early 19th century, Johann Friedrich Meckel was the first to report cases of this *Syndromic Ciliopathy* which was later known as "Meckel Syndrome". Nearly one century later, Gruber published similar observations, while applying the term "*Dysencephalia Splanchnocystica*" (DS) because the condition affects a

plethora of visceral organs leading to the formation of pathologic encystations (Smith et al., 2006; Lu et al., 2013; Barisic et al., 2015). Meckel-Gruber syndrome is a rare fatal autosomal recessive condition that exists more frequently in populations where high consanguinity occurs (Smith et al., 2006; Baala et al., 2007; Lu et al., 2013; Barisic et al., 2015). The disease is mapped to at least a dozen different chromosomal loci (Table 1) (Smith et al., 2006; Baala et al., 2007; Delous et al., 2007; Tallila, Jakkula, Peltonen, Salonen, & Kestilä, 2008; Lu et al., 2013; Barisic et al., 2015; U.S National Library of Medicine, 2018).

Table 1. Genes Associated with Meckel Gruber Syndrome (MGS).

Gene Mutations	Chromosome
MKS1	17q22
TMEM216	11q13
TMEM67	8q
CEP290	12q
RPGRIP1L	16q12.2
CC2D2A	4p15
NPHP3	3q22
TCTN2	12q24.31
B9D1	17p11.2
B9D2	19q13
TMEM231	16q23
KIF14	1q31
TMEM107	17p13

The triad of polycystic kidneys, occipital encephalocele, and postaxial polydactyly are diagnostic (Smith et al., 2006; Lu et al., 2013; Barisic et al., 2015). However, other associated abnormalities may coexist including Oro-facial clefts, genital anomalies and cystic changes in other viscera (Barisic et al., 2015). Failure of the mesodermal induction cascades is incriminated for the pathophysiology of MGS. The cascades occur during early morphogenesis via the orchestrating effect of multiple homeobox genes and growth factors, in addition to the regulation of Hedgehog signalling, ciliary protein localisation and ciliary motility, and ciliogenesis (Dowdle et al., 2011; Abdelhamed et al., 2013; Barisic et al., 2015). The exact prevalence of MGS in the region of the Middle East has not been adequately estimated (Abdelhamed et al., 2013; Barisic et al., 2015). Besides, there are no documented cases in literature from Iraq (Smith et al., 2006; Baala et al., 2007; Delous et al., 2007; Tallila, Jakkula, Peltonen, Salonen, & Kestilä, 2008; Lu et al., 2013; Barisic et al., 2015; U.S National Library of Medicine, 2018). Prospectively, the digital exploration of trends database, via machine learning algorithms, will make a substantial impact on the epidemiologic studies of this condition (Nasrabadi, 2007; Gašević, Dawson, & Siemens, 2015; Hay, George, Moyes, & Brownstein, 2016; Poulin, Thompson, & Bryan, 2016; Steele & Chandler, 2016; Witten, Frank, Hall, & Pal, 2016; Al-Imam & Assi, 2018).

2. Materials and Methods

The review of the literature was conducted systematically, from the 1st to the 9th of June 2018, across medical and paramedical electronic databases including PubMed-NCBI, the Cochrane Library, and Elsevier database via predefined Medical Subject Headings (MeSH) terms. The terms used included all possible synonyms for Meckel syndrome, Meckel-Gruber syndrome, Gruber syndrome, Dysencephalia Splanchnocystica, ciliopathies, and syndromic ciliopathies. Those words were also used in combination with Boolean operators (AND, OR, NOT) as well as parenthesis and quotations. The inclusion criteria included studies with free full-text written in English or Arabic language, studies and reports on humans only, including all levels of the hierarchy of evidence-based medical studies from case reports to systematic reviews, and published in the last five to fifteen years.

3. Results

The total number of hits for all databases was 2089963 distributed as 2085668 (NCBI-PubMed), 1052 (The Cochrane Library), and 3243 (Elsevier). The most informative combination of keywords was (Ciliopathies AND

"Meckel syndrome type 1") which generated 63 hits via NCBI-PubMed only (Table 2). Duplicate articles were eliminated, and all filtered manuscripts successfully that passed the exclusion criteria were scanned via CASP critical appraisal tools to assess the validity and reliability of each study to be deemed suitable for inclusion in the review of the literature (Better Value Healthcare Ltd, 2018). Following the application of the inclusion criteria specific to this report, the total number of reference material was restricted to twenty-six. The level-of-evidence of our study is level-2b following the categorisation scheme adopted by the Oxford Centre for Evidence-based Medicine (CEMB) as of May 2016 (Oxford Centre for Evidence-Based Medicine, 2016).

Table 2. Literature Databases and the Number of Hits based on Keywords Search.

	Number of Hits per Database			
Keyword (MeSH terms)	PubMed-NCBI	The Cochrane Library	Elsevier	Total
Ciliopathies	3904	4	12	3920
Meckel syndrome type 1	63	0	14	77
"Meckel syndrome type 1"	63	0	14	77
Case Reports	1913551	999	2250	1916800
Evidence-Based Medicine	156143	48	872	157063
Iraq	11818	1	81	11900
(Ciliopathies AND Meckel syndrome type 1)	63	0	0	63
(Ciliopathies AND "Meckel syndrome type 1")	63	0	0	63
(Ciliopathies AND "Meckel syndrome type 1" AND Iraq)	0	0	0	0
(Ciliopathies AND "Meckel syndrome type 1" AND Iraq AND Evidence-Based Medicine)	0	0	0	0
(Ciliopathies AND "Meckel syndrome type 1" AND Iraq AND "Evidence-Based Medicine")	0	0	0	0
(Ciliopathies AND "Meckel syndrome type 1" AND Iraq AND Case Reports)	0	0	0	0
(Ciliopathies AND "Meckel syndrome type 1" AND Iraq AND "Case Reports")	0	0	0	0
Total Number of Hits	2085668	1052	3243	2089963

4. Discussion

4.1 Discussion of Literature

The combinatory prevalence of cystic renal diseases and associated ciliopathies is estimated to be approximately 1:2000 (Kagan, Dufke, & Gembruch, 2017). The global incidence of Meckel-Gruber syndrome is around 1:140,000 live births while being higher in the Finnish ethnicities (1:9000), the frequency is also towering among Belgians and Bedouins Kuwaitis and being the highest among Gujarati Indians (1:1,300) (Shetty, Alva, Patil, & Shetty, 2012; Parelkar et al., 2013). The syndrome affects individuals from all ethnic backgrounds with an almost equal male-to-female ratio which is consistent with the autosomal recessive pattern of inheritance (Parelkar et al., 2013; Al-Belushi et al., 2016).

Due to the rarity of the disease, there is a lack of representative inferential data concerning other ethnicities including those from the Middle East. MGS does also exist in Arabs inhabiting the northeast of Israeli-occupied territories in Palestine, while the incidence among Israeli Jews is even higher than the worldwide average (1: 50,000) (Shetty, Alva, Patil, & Shetty, 2012; Parelkar et al., 2013; Aalimi et al., 2015; Al-Belushi et al., 2016). Further, genomic analysis of MGS in Arabs revealed marked genetic heterogeneity and displayed novel candidate genes, while in the state of Qatar the incidence (2:1000 live births) in the local population is analogous to reports from communities where consanguinity is remarkably high (above 40%) (Al-Belushi et al., 2016). Barisic and colleagues, via analysis of data accessed via the *European Surveillance of Congenital Anomalies* (EUROCAT) network, inferred that the prevalence of the syndrome (2.6: 100,000 live births) was stable over time although regional differences within Europe were still observed (Barisic et al., 2015).

Our report will be of high value to medical and paramedical professionals as it represents the first documented case of Meckel-Gruber syndrome from Iraq. Meckel syndrome is one of the catastrophic syndromic ciliopathies.

The condition is transmitted genetically from parents via an autosomal recessive pattern of inheritance (Figure 1A). The syndrome is not only rare, but it tends to occur at higher rates in populations where high consanguinity exists as in the case of the developing countries of South America, Africa, Middle and the Far East. Though our case scenario could not be linked to potential mutagenesis due to chemical or radiation exposure following the American invasion of Iraq (the post-Saddam era), future studies should explore ecological and aggregate analyses to (dis) prove this theoretical assumption. Accordingly, it is possible that such cases could be seen on the rise in subsequent generations in Iraq, making it a real public health catastrophe and an economic burden on the healthcare system.

4.2 Case Report

The study was conducted in compliance with the Ethical approval no. 620-73 on the 15th of May 2016 issued by the authority of the local ethical committee and the Institute Review Board (IRB) of the College of Medicine at the University of Baghdad, Iraq. All patients gave their consent to have their cases reported. This case belongs to the post-Saddam era of Iraq and following the American invasion of Iraq in 2003. It belongs to a middle-class family who are permanent residents inhabiting at Baghdad, the capital city of Iraq. The wife suffered from two incidents of miscarriage (induced abortion). Each abortus was a male fetus while having five healthy daughters as visualised on the pedigree chart (Figure 1B). It is unknown if the family had any history of exposure to radiation or hazardous chemicals. There was neither a history of infection nor an improper maternal medicinal or chemical misuse during pregnancy. The parents, aged about 30 years, are closely related healthy couples (Second-degree relative). They have been married for ten years and have five healthy girls. Five years earlier, they had a planned termination of pregnancy which was of a male fetus with multiple congenital anomalies including occipital encephalocele and bilateral multicystic kidney that was wrongly diagnosed as a case of TORCH infection.

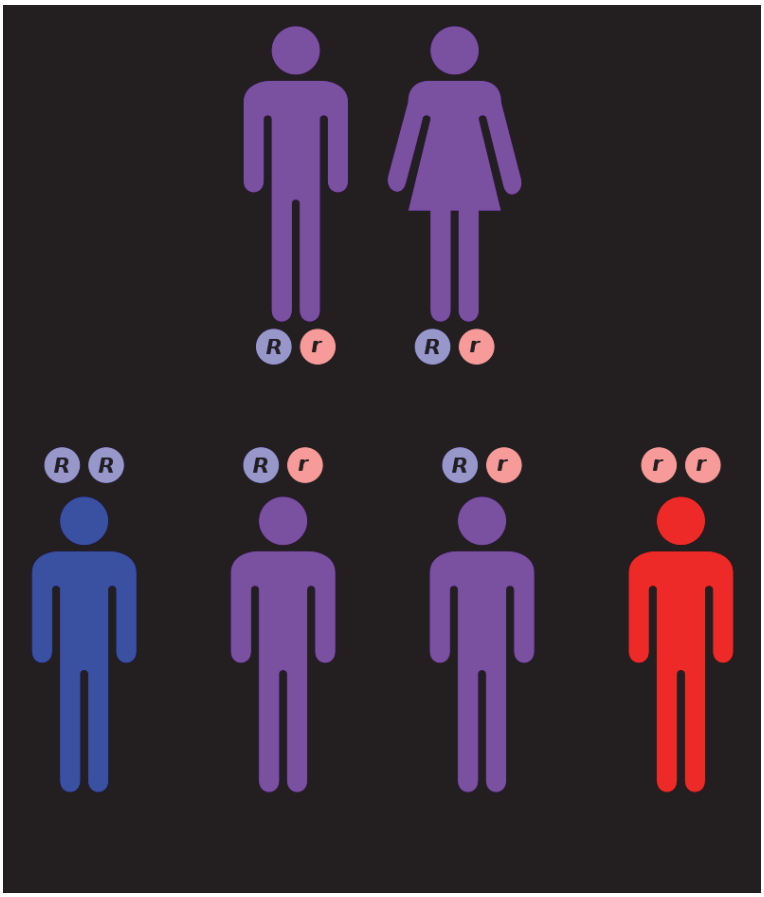

Figure 1A. Schematic Presentation of Recessive Pattern of Inheritance

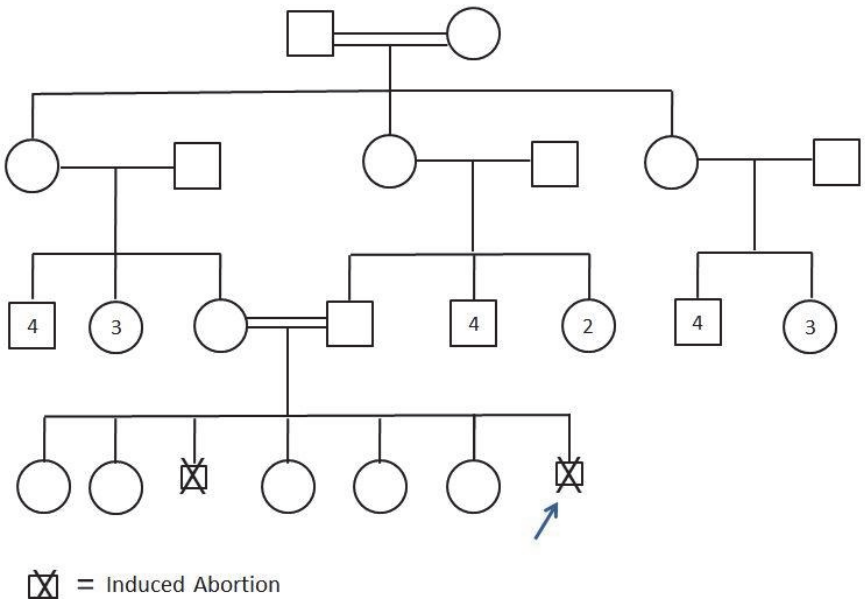

Figure 1B. Pedigree Chart

Recently the wife became pregnant for the seventh time with another male embryo and the family was extremely happy, as they had no male child yet. However, at fourteen weeks of gestation during a prenatal visit, the abdominal ultrasonography confirmed the existence of multiple anomalies affecting the fetus including an occipital encephalocele and bilateral multicystic kidney. According to the ultrasonography, the fetus was estimated to be ageing either 15 or 17 weeks based on fetal length assessment and the biparietal diameters respectively. Fetal body weight was 1600 gm with normal placentation, placental tissue, and amount of amniotic fluid.

However, Doppler ultrasonography of the two umbilical arteries was abnormal. There was a hypoechoic cystic lesion measuring 27 by 30 mm in diameter affecting the occipital region of the head that was diagnosed as an occipital encephalocele. Both kidneys were enlarged and had multiple small cysts within the renal parenchyma. Based on the prior history of abortion and the ultrasonography report, the parents decided to terminate this pregnancy too. A specialist paediatrician examined the aborted fetus which had a diagnostic clinical triad of Meckel–Gruber syndrome including an occipital Encephalocele, bilateral postaxial polydactyly, as well as an abdominal distention of the loins due to visceromegaly affecting the liver, kidneys, and spleen (Figures 2 and 3). The mother had no anomalies affecting the female genital tract as confirmed by the clinical examination, colposcopy, abdominal ultrasonography and hysterosalpingography. Unfortunately, the parents did not allow conducting any laboratory investigations on the aborted fetus, including taking a fetal biopsy, due to social and cultural restraints. Besides, they had to bury the corpse of the fetus in compliance with the medicolegal regulations of Iraq and the religious standards. Future prenatal counselling and genomic analysis, via next-generation sequencing, were advised to the parents. Besides, online databases of trends, including Google Trends, can provide insight into the digital epidemiology of this condition (Al-Imam, 2018). Such information can be of significant value when combined with real-time and predictive analytics based on machine learning technologies (Al-Imam, 2019; Al-Imam, Khalid, Al-Hadithi, & Kaouche, 2019).

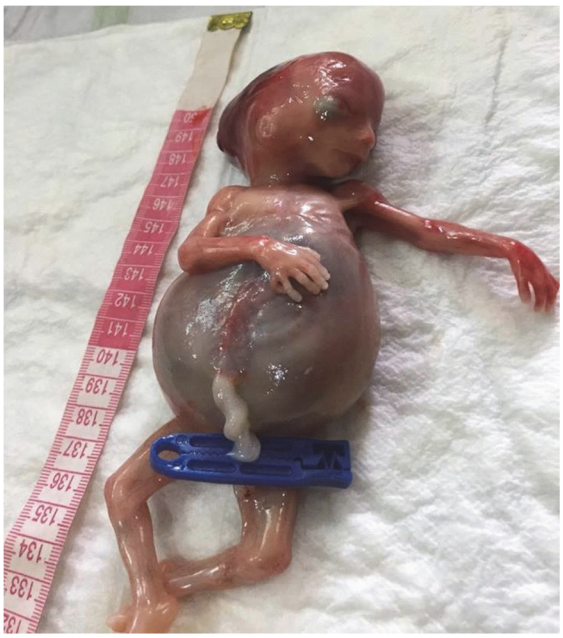

Figure 2. Crown-Heel Length of the Aborted Fetus with Abdominal Distension and Postaxial Polydactyly.
† The clinical photograph is approved for publication (consented).

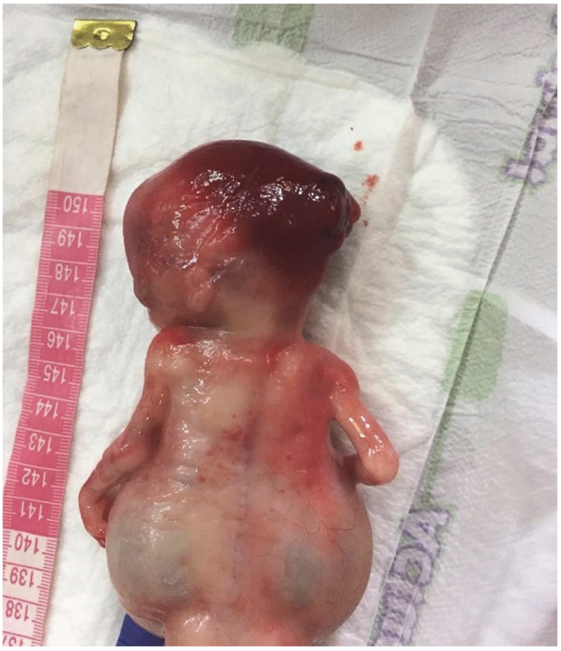

Figure 3. Occipital Encephalocele and Abdominal Distension Most Evident at the Loins (Bilaterally).
† The clinical photograph is approved for publication (consented)

5. Conclusions

Our review and case report represents the first documented paper on Meckel syndrome from Iraq. Concerning the case, there was no potential link to radiological and chemical mutagenesis affecting the genome of the parents who are second-degree relatives. The diagnosis was radiologically confirmed prenatally via serial ultrasonography and clinically after abortion via an experienced specialist paediatrician. Genomic analysis via next-generation and whole exome sequencing is mandatory for detailed knowledge of defective genes affecting the DNA of the parents. Trends databases including Google Trends can be consulted in future studies to assess the extent of digital epidemiology and the relevant geographic mapping of this rare condition. Geographic mapping can evaluate the fractional contribution of the Middle East and Arabic countries to the global map. Besides, Google Trends when

combined with machine learning and data crunching algorithms can extrapolate real-time and predictive analytics of trends. Therefore, it can be integrated into a peremptory warning system to anticipate any change in the interest of surface web users in any rare genetic disease as in the case of Meckel syndrome. The magnitude of benefit of real-time and predictive analytics can be of unique advantage when applied to epidemiological studies via sparing the workforce and financial resources. Future research, via ecological aggregate studies, should also attempt to determine the potential causality of chemical and radiation exposure in inducing genomic instability in this syndrome.

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