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Nonneural Congenital Abnormalities Concurring with Myelomeningocele: Report of 17 Cases and Review of Current Theories

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Key Words
Myelomeningocele, associated anomalies · Congenital malformation · Embryology

Abstract
Objective: Meningomyelocele (MMC) is a common central nervous system birth defect. Various congenital and acquired abnormalities have been reported with MMC, some of which are secondary to the pathophysiology and some are morbidities of the underlying disease. The aim of this study was to discuss current possible theories explaining diverse anomalies/abnormalities seen in a series of 390 patients with MMC. ***Methods:*** A retrospective study was performed using the records of 390 patients with MMC at Children's Hospital Medical Center in Tehran, Iran, from January 2001 to January 2007. A series of 17 cases of MMC with attributed organ anomalies, not explained by a causal effect of the underlying disorder, were compiled. There were 3 cardiac anomalies including ventricular septal defect, pulmonary artery atresia and tetralogy of Fallot, 4 musculoskeletal malformations, consisting of missing rib, polydactylia and complex distal limb anomaly, 4 urological anomalies such as bladder exstrophy, horseshoe kidney and dysplastic kidneys, 2 occipital encephaloceles, 2 congenital adrenal hyperplasia patients with ambiguous genitalia, 1 omphalocele, 1 albinism and 1 Klippel-Feil syndrome. A review of the literature and discussion explaining each of these observations, have been performed and some possible theories have been proposed. ***Conclusions:*** Although various organ anomalies with different embryological origin had been observed and reported with MMC, it is difficult to explain their development using one of the current theories of MMC formation. It could be attributed to a possible genetic defect or merely an incidental finding. A teratological insult during the embryogenic phase would be an alternative assumption.

Introduction

Myelomeningocele (MMC), part of the neural tube defect (NTD) spectrum, is a major congenital anomaly caused by a defective closure of the neural tube between the 18th and 25th days of gestation, resulting in the protrusion of the cord and the meninges through the defective bony encasement of the spinal column [1]. The incidence of MMC varies from 0.4 to 1.91 per 1,000 live births according to the country, culture and socioeconomic status [2], and the reported incidence in Iran is 1.6/1,000 [3].

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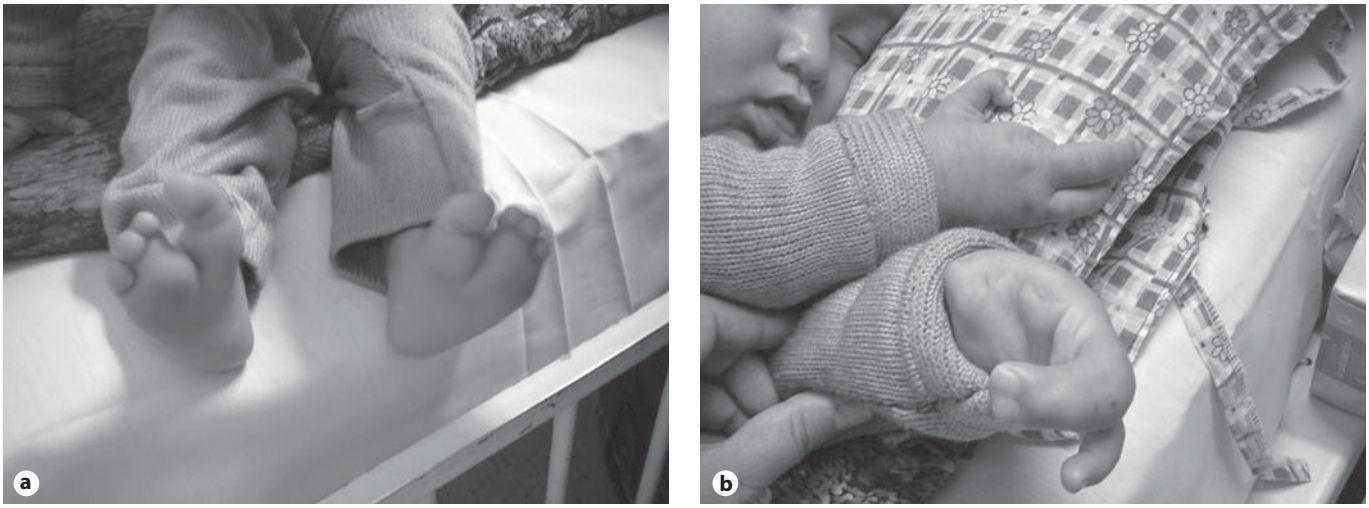

Fig. 1. The child (patient No. 6) with cleft feet (**a**) and longitudinal lateral ray deficiency in both hands (**b**).

According to the most widely supported theory of spina bifida formation, the posterior neuropore fails to close completely during neurulation, and an MMC, Chiari II malformation and hydrocephalus develop [4].

There have been several associated abnormalities that could be interpreted by the course of the disease. Arnold-Chiari II malformation [5], syringomyelia and hydrocephalus [6] are related to the pathogenesis of MMC, whereas some problems are considered as primary or secondary consequence. Neurogenic bladder [7, 8], cryptorchidism [9], club foot [10], spinal deformity [11] and congenital dysplasia of the hip [12], bone fractures [13], sexual problems [14], precocious puberty [15], deep-vein thrombosis [16] and latex sensitization [17] are a few examples of the known complications due to MMC and are beyond the scope of the current article.

In the following we present a series of 17 cases of MMC with attributed organ anomalies, not explained by a causal effect of the underlying disorder. The current theories describing the etiology of such anomalies and a possible coherence with MMC are also discussed.

Patients and Methods

A retrospective study was conducted of the records of 390 children who were diagnosed and managed as MMC in the neurosurgery department of the Children's Hospital Medical Center in Tehran between January 2001 and January 2007. All cases had been admitted to the neurosurgery ward and had undergone complete physical examination as well as radiological studies with respect to neurological disabilities. In cases with clinical findings suggestive of concurrent medical problems, appropriate paraclinical studies including e.g. echocardiography or abdominal sonography had been carried out.

Of all reviewed records a series of 17 cases with anomalies unrelated to their MMC, which could not be categorized as a syndrome either, were compiled. The study was carried out in accordance with the ethical guidelines for retrospective chart review in place at the time.

Results

Demographic Characteristics

Among 17 patients there were 7 males, 8 females and 2 neonates with ambiguous genitalia. The mean age was 4.3 months and varied from 5 days to 3 years. There was no sufficient data about maternal prenatal care. All pregnancies had been uneventful. None had been diagnosed as MMC prenatally.

MMC Pattern and Neurological Features

With regard to the location of MMC, there were 6 (35.2%) lumbosacral, 4 (23.6%) thoracolumbar, 3 (17.6%) lumbar, 2 (11.8%) cervical and 1 (5.9%) thoracic lesion, and 1 (5.9%) patient presented with a sacral MMC. Their neurological examination revealed paraplegia in 7/17 (41.1%) cases, distal weakness in 8/17 (47%) and 2/17 (11.9%) had normal motor findings.

Table 1. Observed associated congenital anomalies with MMC (17 patients)

Patient	Age	Sex	Spinal level	Neurological evaluation	Associated anomaly	Outcome
1	7 months	F	TL	paraplegia	albinism, hydrocephalus	MMC repaired
2	10 days	F	LS	paraplegia	occipital encephalocele	MMC repaired
3	2 months	M	L	distal leg weakness	tetralogy of Fallot	Not repaired
4	6 months	F	TL	paraplegia	lack of 4 ribs	MMC repaired
5	20 days	AM	S	distal leg weakness	CAH	MMC repaired
6	2 months	F	C	normal	polydactylia	MMC repaired
7	10 days	F	C	normal	pulmonary artery atresia	MMC repaired
8	4 months	F	TL	paraplegia	Klippel-Feil syndrome	MMC repaired
9	25 days	M	L	distal leg weakness	occipital encephalocele	MMC repaired
10	6 months	M	LS	distal leg weakness	4 limbs anomaly	MMC repaired
11	2 months	M	TL	paraplegia	lack of 5 ribs + horseshoe kidney	MMC repaired
12	3 months	M	TL	paraplegia	dysplastic kidney	MMC repaired
13	5 days	AM	LS	distal leg weakness	CAH	MMC repaired
14	2 months	F	LS	distal leg weakness	VSD	MMC repaired
15	10 days	F	LS	distal leg weakness	omphalocele	MMC repaired
16	3 years	M	L	paraplegia	bladder exstrophy	Not repaired
17	3 years	F	LS	distal leg weakness	bladder exstrophy	MMC repaired

AM = Ambiguous; C = cervical; CAH = congenital adrenal hyperplasia; F = female; L = lumbar; LS = lumbosacral; M = male; S = sacral; TL = thoracolumbar; VSD = ventricular septal defect.

Associated Anomalies

Of a total of 17 patients, there were 3 cardiac anomalies including ventricular septal defect, pulmonary artery atresia and tetralogy of Fallot. Four had musculoskeletal malformations consisting of missing rib, polydactylia and complex limb anomaly (fig. 1). Urological anomalies such as bladder exstrophy, horseshoe kidney, and dysplastic kidneys were seen in 4 patients. Occipital encephalocele was seen in 2 of our cases. There were 2 patients with documented congenital adrenal hyperplasia (CAH) who presented with ambiguous genitalia, 1 case of omphalocele, 1 with albinism and 1 with Klippel-Feil syndrome. The demographic and clinical characteristics of the patients included in the study are summarized in table 1.

All patients were managed surgically except for 2 cases because of compromised cardiac condition and parent refusal of surgery. Ventriculoperitoneal shunting was performed for 2 patients with severe hydrocephalus.

Discussion

MMC is just one manifestation of a malformation that affects the entire central nervous system. According to the most widely supported theory of spina bifida formation, the posterior neuropore fails to close completely during neurulation, and an MMC, Chiari II malformation and hydrocephalus develop. The association with nutritional deficiencies, particularly folate and zinc, the use of anticonvulsants and maternal diabetes mellitus as well as other possible factors have been demonstrated [4]. Most are located in the caudal thoracolumbar spine or more distally (85%) [4].

With regard to various pathophysiological interactions leading to MMC, the association with other congenital anomalies that could have been initiated in the same embryological phase or have happened as a consequence is not unexpected. As such, Arnold-Chiari malformation type II, hydrocephalus, bladder and bowel incontinence, and paraplegia are direct complications of the underlying disease. Associated anomalies reported with greatest frequency (1–6%) are facial clefting, cardiac defects, limb reduction defects, anophthalmia/microphthalmia, abdominal wall defects and renal anomalies [18, 19]. Yet, as illustrated in our series, some malformations are not explicable as causal or secondary consequence of MMC. Here we categorized the detected abnormalities in this series and discussed the possible correlation with the most recent theories of MMC formation.

As the theory of 'overdistention' explains, MMC occurs at the end of week 4 of the development if the neural

tube fails to close spontaneously. If overproduction of spinal fluid occurs at this stage of development, the neural tube distends, ruptures and spinal fluid can infiltrate the surrounding mesoderm destroying neural crest cells [20]. The neural crest cells play an important role in forming mesodermal organs such as the heart, kidney and skeletal system; thus, their destruction may prevent the normal development of both spinal cord and the above structures [21].

Although no specific gene involvement has been identified, many of the related mutations have been accompanied by other organ anomalies such as hydrocephalus, ocular, renal, cardiovascular and skeletal defects [22].

It has been reported that rib fusion is the most common type of rib anomaly in association with other congenital malformations [23]. The fact that an NTD develops in the first 4 weeks and rib development begins not sooner than week 9 of gestation [24] explains why we only found a rib missing in 390 patients of MMC and not rib fusion.

It is also known that renal abnormalities including renal agenesis and horseshoe kidney are more often associated with MMC [25, 26]. The joint occurrence of genitourinary anomalies and NTDs could suggest a midline fusion defect that might have a unique genetic mechanism, possibly X-linked [27]. This genetic association is well defined in Meckel-Greuber syndrome, a lethal autosomal recessive disorder with known chromosomal alterations, in which occipital encephalocele accompanies renal anomalies such as horseshoe kidney.

In genetic perspective, many animal models have been carried out to determine the culprit gene for kidney and urinary tract anomalies and some chromosomal defects and gene patterns such as Bmp4 have been shown to contribute to the susceptibility for NTD formation. Some human genes, especially members of *PAX* and *HOX* genes, have also been concurrently observed to be involved in the development of both NTDs and renal defects, in particular renal agenesis [22, 28, 29].

Cardiac anomalies have been reported to be more common in association with MMC [30]. Atrial septal defect has been the most common malformation, whereas in our study there was 1 case of ventricular septal defect, 1 tetralogy of Fallot and 1 pulmonary artery atresia never reported before.

Other observations could support the causal association of NTD with cardiac anomalies, midline structures and body wall defects. First, both the heart and central nervous system rely on homocysteine for their normal development [31]. Moreover, as the theory of 'space limitation' states, shortening of the trunk and cervical retroflexion accompany cranial and upper spinal NTDs and impose a space limitation on the abdomen and thorax which might result in abdominal wall defects (principally omphalocele), bladder exstrophy and possibly cardiac defects [32]. However, the 'space limitation' theory does not explain the correlation of body wall defect with lower spinal NTD as observed in our patients. Two recent theories, the 'schisis association' and 'midline developmental field concept', have also proposed an explanation of the etiology of co-occurring NTDs and midline structure defects [33, 34].

A genetic correlation between cardiac and neural tube abnormalities has already been demonstrated. Accordingly, disruption of the *Sufu* gene has been shown in animal models to be responsible for both cardiac defects and NTDs, and Dishevelled 2 *(Dvl2)* gene disruption has caused the same simultaneous abnormalities in similar human studies [35, 36]. Recent discoveries have suggested a possible etiological role for the environmental factors. As such, periconceptional intake of multivitamin supplements containing folic acid may reduce the risk of congenital cardiovascular defects in offspring, similar to the known risk reduction for NTDs seen with folic acid, whereas high vitamin A in the diet and/or supplements can result in disturbances of neural crest cells (i.e. cardiac and noncardiac defects) or outflow tract [37].

The theory of NTD formation proposed by Van Allen et al. [38] entitled 'multi-site closure model' and the recently modified version suggested by Padmanabhan [22], which explain 5 and 3 closure sites for the neural tube, respectively, can explain the development of encephaloceles in 2 of our patients with lumbar and lumbosacral MMCs.

Klippel-Feil syndrome, which results from failure of normal segmentation of the somites during the 3rd to 8th weeks of gestation, can be complicated with cervical spina bifida as the most common associated central nervous system and axial anomaly [39–41]. Opposed to our expectations, our patient suffered from MMC at the thoracolumbar instead of cervical level. Hypothetically, with regard to embryogenesis, both MMC and Klippel-Feil syndrome could result from an insult within the first 4–5 weeks of gestation. So a teratogenic theory can be postulated.

MMC can probably be associated with pigmentation disorders due to specific gene defects. Of these pigmentation disturbances, Waardenburg syndrome (WS) is the most correlated example which is associated with MMC through *PAX* gene rearrangement [42]. WS consists of

prominent nasal root, deafness and pigmentation disturbances with or without dystropia canthorum [43, 44]. The pigmentation disturbance can be in the spectrum of albinism [45]. Ocular albinism, a part of pigmentation disturbances seen in WS, is a mild form of oculocutaneous albinism which was present in our patient. So we believe that oculocutaneous albinism is a manifestation of WS, but since WS is a rare entity and other phenotypical features of WS were not present, we did not perform an extensive analysis to confirm this diagnosis.

Congenital adrenal hyperplasia (CAH) is a collective term that refers to a series of autosomal recessive disorders that are associated with genetic defects in cortisol biosynthesis [46]. Collipp et al. [47] reported different anomalies in their CAH cases including cardiovascular anomalies, the most observed, genitourinary tract anomalies, midline body wall defects and gastrointestinal tract anomalies. There are also some reports on the relationship between renal anomalies and CAH [48, 49].

The association of the above disease with MMC has never been reported before. Although endocrine studies have been performed in children with MMC, most of them have focused on hydrocephalus resulting from MMC and proceeding pituitary dysfunction [50]. Several lines of evidence suggest a genetic component for NTDs [51]. Animal studies have shown that there are as many as 100 mutant genes affecting neurulation and almost all of them have their homologs in humans [52, 53]. NTDs are associated with known genetic syndromes, whereas chromosome abnormalities, specifically aneuploidy, are found in 5–17% of cases with NTDs [51]. Recently, whole-genome-wide linkage screening in NTDs revealed regions of interest on chromosomes 2, 7 and 10 [54, 55].

Considering these observations, some mutations on chromosomes which are involved in the pathogenesis of albinism or CAH may be responsible for the development of MMC [54, 55]. For example, mutations in the *Macs* gene in the mouse lead to exencephaly and other midline NTDs; its human homolog *MACS* has been localized to chromosome 6 [51], the same chromosome involved in the pathogenesis of CAH.

Limb deformities (mainly limb reduction) associated with MMC have also been reported before [26]. The limb bud appears in about the 4th week of gestation, so a teratological insult may be the main culprit. However, it is difficult to consider such a relationship between hand or foot deformities and MMC.

Split-hand/split-foot malformation (SHFM), also known as ectrodactyly, is a congenital limb malformation, characterized by a deep median cleft of the hand and/or the foot because of the absence of central rays. It can occur as a single entity or as a part of a syndrome. Both forms are frequently found in association with chromosomal rearrangement such as deletions or translocations. Several SHFM loci have been mapped, including SHFM1 (7q21), SHFM2 (Xq26), SHFM3 (10q24), SHFM4 (3q27) and SHFM5 (2q31).

More than 50 related syndromes are distinguished which are thought to be due to genetic factors or to exposure of the embryo to environmental factors. Syndromes in which ectrodactyly is associated with other abnormalities can occur when 2 or more genes are affected in a chromosomal rearrangement, where alterations in chromosome 2q31 and 7q21 have been discussed more extensively [56, 57].

In contrast, syndromic ectrodactyly may also be the result of single gene defects like the syndrome of ectrodactyly, ectodermal dysplasia and clefting of the lip/palate (EEC syndrome) [57].

None of these syndromes include MMC or even an abnormality within the NTD spectrum. Although many animal studies have been carried out to propose candidate genes for the pathogenesis of NTDs, the results are not satisfying, and so far, only few regions have mainly been suspected of being involved in the pathogenesis of NTD in humans which are located on different parts of the human genome. Among these regions, *PAX* genes are of particular interest. As discussed above, we think that mutation in these genes, *PAX3* in particular, could be a cause of the development of both albinism and MMC in a single case. The *PAX3* gene is located on 2q35–36.2, and deletion of this region is reportedly associated with MMC. So a fairly large chromosomal rearrangement in the 2q area which involves both 2q31 and 2q35 regions could be considered as the underlying reason for observing such a limb anomaly along with MMC. However, a thorough genome-wide screening is required to confirm this hypothesis. On the other hand, to depict a syndrome, more cases are needed, and a detailed investigation should be designed which is beyond the scope of the current study.

Regarding the proposed theories of MMC formation together with our observations, it seems reasonable to consider a common embryological basis or unknown teratological insult, in a vulnerable genetic background, for this association, while the probability of a mere coincidence or being part of a new congenital syndrome cannot be ruled out. However, the authenticity of this claim is yet to be determined.

Conclusion

Although various organ anomalies with different embryological origins had been seen with MMC, it seems almost impossible to explain all their correlations with current theories. Regarding the existing literature, the association of cardiac, renal, skeletal and body wall defects with MMC can be reasonably explained by genetic and environmental assaults, yet there are some ambiguities why certain anomalies like horseshoe kidney are more commonly observed with MMC. Since we observed 2 not previously reported CAH cases with MMC, more extensive genetic investigation is recommended in future reports. In addition, it seems that MMC patients with pigmentation disorders and limb anomalies need further evaluation for possible chromosomal rearrangements.

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