

Commentary on Aplasia cutis congenita in monozygotic twins: What should we do further?

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Commentary

Aplasia cutis congenita (ACC) is a rare congenital anomaly characterized by a localized or widespread lack of skin at birth [1]. Most information about ACC exists as individual case reports and medium-sized studies. Recently, a study based on the European network of population-based registries for congenital anomalies (EUROCAT) showed that the scalp is the most common site of ACC (96.4%), and 33.8% of cases have related congenital abnormalities. Patau and Adams-Oliver syndromes are the most common among the associated chromosomal anomalies (88.3%) and the associated genetic syndromes (57.7%) [2].

In previous case reports, the majority of cases are individual occurrences, however, when the phenomenon occurs in monozygotic twins, it becomes a more extraordinary and thought-provoking phenomenon. The paper of the two ACC affected monozygotic twin boys provides the clinical features, dermoscopic findings, and healing process of the ACC lesions in twins, contributing to the understanding of the condition in this specific context, and a clinical report for the rare event of ACC in twins [3].

ACC is considered to be a congenital malformation associated with both genetic and environmental factor contributions [4]. The exact cause of ACC in monozygotic twins is not fully understood. However, it is believed that disruptions in embryonic development could play a role [5]. The formation of the skin during early gestation involves complex processes and any disturbances during this critical period could result in the absence of skin in affected areas. It is thought that ectoderm dysplasia (ED) might underlie the occurrence and development of ACC [6] while ectodysplasin A (EDA) signaling has been identified as regulating the morphogenesis of skin appendages [7].

EDA signaling is mediated by EDA, receptor EDAR, and EDAR-associated via death domain EDARADD, which form a unique TNF ligand–receptor–adapter protein complex mainly restricted to the skin appendages of vertebrates [8]. In humans, mutations in any of these three genes lead to ED, featured by the lack, or malformation of, one or more skin appendages including hair follicles, nails, teeth, eccrine sweat glands, and Meibomian glands. However, research about EDA signaling in ACC is lacking.

Interestingly, a few cases of ACC with bone dysplasia have been reported, the author speculated that the skin defect covering bone growth was inhibited due to the loss of osteogenesis stimulators from the dermal fibroblasts, endothelial and appendage-derived cells [9]. It has been found that ribosome biogenesis factor (BMS1) gene mutations are present in some cases of ACC. BMS1, that affects ribosomal function, can cause skin fibroblast cell cycle defects and a reduced cell proliferation

rate due to a p21-mediated G1/S phase transition delay, indicating a central role of increased p21 levels for the ACC phenotype [10].

In the case of monozygotic twins, their genetic makeup is nearly identical [11], suggesting that both twins would likely carry the same predisposing genes when a genetic predisposition is involved in the development of ACC. However, monozygotic twins might still experience differences in their intrauterine environments even when they share a similar genetic background [12]. These differences can arise due to variations in blood supply, amniotic fluid levels, or other factors that could affect the development of specific body parts, including the skin.

The study in the paper performed high-throughput sequencing for the twins and their family and did not find a clear pathogenic variant that was clinically relevant to the subjects, so the author proposed that placental bloodflow insufficiency related to gestational diabetes mellitus might play a role in the development of the ACC [12]. The notable pathogenic factor during pregnancy for the abnormality was the mother's type 2 diabetes. It is believed that the gestational diabetes could cause placental dysfunction [13], and a compromised placenta restricts fetal blood supply would impede normal fetal growth [14]. Remarkably, it has been shown that the impaired fetal vascular perfusion due to a severe placental disorder might be induced by maternal diabetes, umbilical cord obstruction, fetal cardiac insufficiency, and a propensity for thrombosis formation [15]. Therefore, the suboptimal fetal development representing fetal growth restriction, is a common consequence of the inadequate blood flow [16]. So, the authors hypothesized that insufficient placental blood flow associated with gestational diabetes could be a potential factor for the development of ACC.

In addition, in some cases of monozygotic twins, there can be complications such as twin-to-twin transfusion syndrome (TTTS) [17]. TTTS is a condition in which there is an imbalance in blood flow between the twins, leading to one twin receiving more blood than the other [18]. This could potentially impact the development of both twins and might be related to the occurrence of ACC in one or both of them.

Above all, the occurrence of ACC in monozygotic twins raises questions about the interplay between genetic factors, embryonic development, and the intrauterine environment. It points out the complexity of human development and the need for further research to better understand and manage such rare congenital conditions. Indeed, studying these cases may offer insights into the underlying mechanisms that contribute to ACC and related congenital malformations. ACC can be associated with incomplete development of the skull, bones, and dura mater; they can be life-threatening, though these complications are infrequent. Therefore, it is necessary to initiate a comprehensive assessment to determine early intervention [19], and to further develop the knowledge and awareness of these rare congenital conditions.

Dermatoscope and histopathology examination, and genomic detection, when necessary, are the main approaches to the evaluation and management of the anomaly. So far, there is no consensus on the treatments for ACC between conservative and surgical methods. Therefore, we emphasize the importance of early inspection and close follow-up for ACC; the means to manage the congenital condition may depend on the dimension and location of the lesion, the related complications, and the constitution of the victims.

Finally, we advocate that whole population education and preconception care implementation would be a crucial policy priority for the primary prevention, or minimization, of adverse consequences due to ACC, given that the optimal preconception health is associated with improved pediatric outcomes through risk screening, motivational counseling, disease optimization and specialist referral as appropriate [20]. Education for health professionals and policy makers would optimize the disease risk controlling factors, promote the condition management, and improve the outcomes for those affected by ACC.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Author Contributions

Hui-Jun Lai: Data curation (equal); writing—original draft (equal). Ping-Ping Ma: Data curation (supporting); writing—review & editing (supporting). Mei-Yan Lai: Formal analysis (supporting); writing—review & editing (supporting). Hong-Wei Guo: Formal analysis (equal); writing—review & editing (equal).

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