Aplasia cutis congenita: three cases with three different underlying etiologies

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Aplasia cutis congenita (ACC) is an uncommon condition in which localized or widespread areas of skin are absent or scarred at birth. There is no single underlying cause of ACC, as it simply represents a physical finding that reflects a disruption of intrauterine skin development. Here we report three cases of ACC of the scalp with three different etiologies: congenital rubella syndrome, trisomy 13 and fetal valproate syndrome. The aim of the present report is to increase awareness of these skin defects and emphasize the importance of underlying etiologies.

Key words: aplasia cutis congenita, trisomy 13, fetal valproate syndrome.

Aplasia cutis congenita (ACC) is a rare congenital skin defect that may be localized or may affect wide areas of the body[1,2]. ACC is a developmental absence of skin characterized by well-demarcated, oval or circular ulcers or scars, and it may present with solitary or multiple lesions[1,2]. ACC is primarily a clinical diagnosis, with no specific histologic alterations. The scalp vertex is the most commonly involved site (nearly 90%); only about 10-15% of ACC occur in other body areas[3,4]. At birth, most cases of ACC have ulcerated lesions, which may show total absence of all layers of skin, extending to the bone or dura[3]. ACC is not only a physical sign but may provide a clue to an underlying disorder. Most individuals with ACC have no associated abnormalities, but it can also be associated with other congenital malformations, intrauterine infections, chromosomal anomalies, or other disorders such as ectodermal dysplasia and epidermolysis bullosa[5-9].

Here we report three cases of ACC of the scalp with three different etiologies - congenital rubella syndrome, trisomy 13 and fetal valproate syndrome, and we review the differential diagnosis for ACC.

Case Reports

Case 1

A 13-day-old female was admitted to the hospital with a cardiac murmur and scalp defect. She was the second child of a 28-year-old gravida 2, para 2 mother and a 35-year-old father, who were nonconsanguineous. The mother had a history of generalized maculopapular rash in the third month of her pregnancy. She was suspected of having a viral infection but no serological tests were performed.

On physical examination of the patient, weight, length, and head circumference were all below the 3rd centile (2400 g, 46 cm and 31 cm, respectively). She had prominent epicanthic folds, low-set ears, bilateral camptodactyly, and absence of skin on two adjacent parts of the scalp: a 0.5x0.5 cm annular, atrophic lesion and a 1x1 cm oval well-demarcated, crusted ulcer (Fig. 1). Echocardiography revealed secundum atrial septal defect and patent ductus arteriosus. Cranial magnetic resonance imaging (MRI) revealed partial corpus callosum agenesis. According to her serological tests, rubella IgM

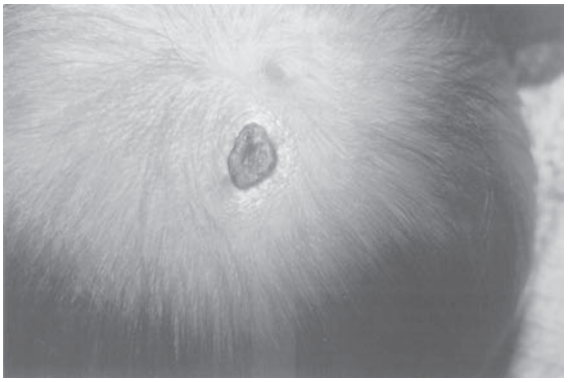

Fig. 1. Case 1 - ACC on the vertex of the scalp.

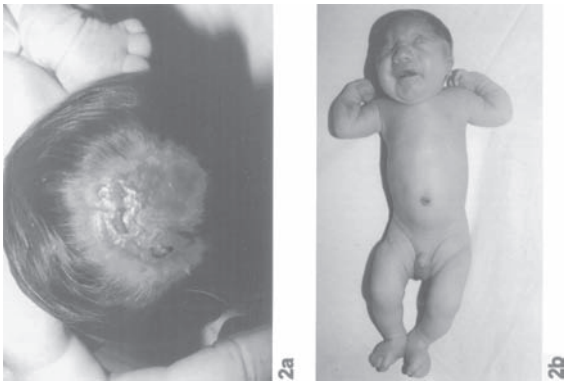

Fig. 2a. Case 2 - A site of ACC on the vertex of the scalp. 2b. Clinical aspect of Case 2.

and IgG were positive, toxoplasmosis IgM and IgG were negative, cytomegalovirus IgM was negative and IgG was positive, and herpes simplex type 2 IgM and IgG were negative. Karyotype analysis of the patient was 46,XX. Her mother's serological tests showed positive rubella IgG and negative rubella IgM. Her auditory evoked potential revealed mild type sensory neural deafness. Her ophthalmological examination was normal. Serologic tests of the infant for rubella were repeated in the third month of life. IgM was found negative and IgG positive, with a slightly higher titer than at the first testing. These findings were consistent with a diagnosis of intrauterine infection with rubella virus.

Case 2

A 17-day-old term male infant was referred for evaluation of facial dysmorphism and scalp defect. His parents were healthy and non-consanguineous. The family history was unremarkable. On physical examination, his weight was 3300 g (3rd centile), length was 49 cm (50th centile) and head circumference was 33 cm (<3rd centile). His anterior and posterior fontanels were 2x2 cm. Dermatologic examination revealed a wide, circular well-demarcated non-inflammatory ulcerative 3 cm scalp defect (Fig. 2a). There was an underlying bony defect. He had frontal bossing, downslanting palpebral fissures, wide nasal root, microphthalmic right eye, bilateral cataracts, bilateral retinal dysplasia, submucous cleft of the palate, low-set ears, bilateral external ear abnormalities, and short neck (Fig. 2b). He had a grade 3/6 systolic murmur over the entire precordium, a micropenis and phimosis. There were flexion contractures of both hands, bilateral pes planus, and increased space between the first and second toes, bilaterally. Echocardiography revealed transposition of the great arteries, double outlet right ventricle, atrial and ventricle septal defects, and mitral insufficiency. Cranial MRI revealed bilateral symmetrical T2-FLAIR hyperintense lesions on the nucleus caudatus and lentiformis. Splenium and genu of corpus callosum were absent. A scalp defect without skin and fat tissue was noted on MRI and no skull was revealed under the defect area. Mega cisterna magna was noted. His chromosomal study showed 47, XY, +13.

Case 3

A one-day-old female full-term newborn was admitted to the hospital for evaluation of a systolic murmur. She was born by cesarean section to a 20-year-old gravida 1, para 1 epileptic mother who had used valproic acid and carbamazepine throughout her pregnancy. The parents were nonconsanguineous. On physical examination, her weight was 2600 g (3-10th centile), length 47 cm (3-10th centile) and head circumference 32.5 cm (3rd centile). She had a well-demarcated oval-shaped scalp defect with an area of 0.5 x 0.5 cm (Fig. 3), micrognathia, epicanthus inversus, bilateral coloboma of the irides, clinodactyly, weak femoral pulses, hepatomegaly, and a grade 3/6 systolic murmur over the entire precordium. The two-dimensional echocardiography and computerized tomography revealed hypoplastic aortic arch, aortic coarctation, aberrant right subclavian artery, ventricular septal defect, secundum atrial septal defect and patent ductus arteriosus.

Fig. 3. Case 3 - Two areas of ACC.

On the 7th day of admittance, the baby had hepatomegaly, respiratory distress and metabolic acidosis. She was intubated and put on mechanical ventilation. Her condition deteriorated and she died on the 13th day of life. She was diagnosed with probable fetal valproate syndrome.

Discussion

Aplasia cutis congenita was first reported by Campell in 1826[1]. Since then, there have been a number of cases reported in the literature. The incidence of ACC in liveborns has been reported as nearly 2.8 cases per 10,000[10]. Frieden[9] classified ACC into nine groups based on the site of skin defect, presence or absence of other malformations, and pattern of inheritance. The etiology of ACC may be genetic or non-genetic (Table I), as illustrated by our patients. ACC is most often a benign isolated skin defect, but it can occur with other physical anomalies or malformation syndromes (Table II). Recently, Zehnaly et al.[11] showed that development of a skin defect of the scalp in mice resulted from the loss of the TGF-beta type II receptor. Thus, they implied that this gene was a candidate gene for ACC. Focal dermal hypoplasia (FDH), also known as Goltz syndrome, is an X-linked disorder with a developmental skin malformation like ACC, but can be distinguished from ACC by the presence of patchy dermal hypoplasia with herniation of subcutaneous tissues, and papillomas, which often conform to a Blaschko-linear pattern. Recently, investigators found FDH associated with the mutations of the PORCN gene[12,13].

Our first case illustrates an etiology of ACC related to intrauterine infection, in this case rubella. Other infections during the intrauterine period that have also been reported as underlying causes of ACC include herpes simplex virus or varicella[9,14]. Congenital rubella syndrome was the first virus demonstrated to be a teratogen. The risk of congenital anomalies in liveborn children with intrauterine exposure to rubella virus varies with a number of factors, the most important of which is the stage of pregnancy. Exposure in the first trimester is the highest risk period for teratogen effect from fetal rubella infectious, causing major anomalies in 38-100%[15]. Our patient's developmental manifestations as scalp defect and cardiac/central nervous system malformations,

Table I. Disorders Associated with ACC

Causes	Examples
1. Chromosomal	Trisomy 13, Del (4p) syndrome, Tetrasomy 12p
2. Monogenic	
a) Autosomal Dominant	Adams-Oliver syndrome, Autosomal dominant ACC, Ectrodactyly-ectodermal dysplasia-clefting syndrome, Ectodermal dysplasia, Scalp-Ear-Nipple syndrome
b) Autosomal	Recessive Autosomal recessive ACC, Johanson-Blizzard syndrome, Setleis syndrome, Ectodermal dysplasia-clefting syndrome, Epidermolysis bullosa*
c) X-Linked	Goltz-Gorlin syndrome (focal dermal hypoplasia), MIDAS (Microphthalmia, Dermal Aplasia and Sclerocornea) syndrome
3) Teratological/Exogenous	Alcohol, cocaine, marijuana, methimazole, misoprostol, Congenital infections (herpes simplex, rubella, varicella), Amniotic band disruption complex

*Simplex, junctional, or dystrophic types of epidermolysis bullosa. Adapted from Evers[8].

Table II. The Abnormalities Most Commonly Associated with ACC

Region	Anomalies
1. Head and neck	Facial abnormalities (i.e. cleft lip/palate), wooly hair, cranial arteriovenous malformation, hemangioma, skin tags, microphthalmia, corneal opacities, eyelid colobomas, cranial stenosis, leptomeningeal angiomatosis
2. Abdomen and internal organ abnormalities	Supernumerary nipples, absent breasts, heart defects, renal abnormalities,
	Pyloric or duodenal atresia, ureteral stenosis, gastroschisis, omphalocele, pancreatic insufficiency, double cervix and uterus
3. Limbs	Limb hypoplasia or amputation, hypoplastic or absent distal phalanges, nail hypoplasia or dysplasia, polydactyly, limb position defects (i.e. club foot), arthrogryposis, spastic paralysis
4. Other	Psychomotor retardation, seizures, spinal dysraphism, persistent cutis marmorata

Adapted from Frieden.[9]

together with a maternal history of generalized maculopapular rash in the third month of her pregnancy, suggest a viral (rubella) exposure in the early periods of pregnancy.

Our second case illustrates a chromosomal anomaly as an etiology of ACC: trisomy 13 syndrome. Scalp ACC is found in 50% of newborns with this disorder and the defects are generally 0.5 cm in size; however, they can be very large[9,16]. Chromosomal analysis is indicated in any child with scalp ACC, especially if associated with multiple congenital anomalies when a specific syndrome is not identified.

A few cases of ACC have been reported in newborns with in utero exposure to antithyroids, methimazole, carbimazole, and misoprostol. Hubert et al.[7] also reported a newborn with isolated ACC whose mother had been treated with valproic acid during her pregnancy. Although the mother in this case had been treated with the combination of valproate and carbamazepine, our patient's clinical findings were compatible with fetal valproate syndrome. Children exposed to polytherapy for epilepsy containing valproate usually have dysmorphic features related to the valproate exposure[7]. Therefore, the scalp defect and dysmorphic findings observed in the third case may have been a consequence of intrauterine exposure to valproic acid.

In conclusion, we present three etiologies of ACC and review the differential diagnosis. ACC is generally an isolated skin defect; however, intrauterine infectious, genetic, and other teratogenic factors should be investigated, especially when ACC is associated with dysmorphic findings and cardiac defects.

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