Generalized arterial calcification of infancy and pseudoxanthoma elasticum: two sides of the same coin

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GACI AND ENPP1 MUTATIONS

Generalized arterial calcification of infancy (GACI; OMIM 173335) is a rare autosomal recessive disease, which is characterized by severe calcification of the internal elastic lamina in large- and medium-sized arteries associated with intimal proliferation leading to arterial stenoses and heart failure within the first months of life. Although survival to adulthood has been reported, GACI is often lethal in the first 6 months of life. In the past, few patients survived the neonatal period (Moran, 1975; Morton, 1978), whereas more recently, patients treated with bisphosphonates have experienced a more favorable outcome (Rutsch et al., 2008; Ramjan et al., 2009). Some patients may also develop hypophosphatemic rickets with hyperphosphaturia, a finding associated with improved survival beyond infancy in patients with GACI (Rutsch et al., 2008; Levy-Litian et al., 2010; Lorenz-Depiereux et al., 2010). The disease has been found to be caused by inactivating mutations in ENPP1 (MIM 173335; Rutsch et al., 2003). ENPP1 encodes the ecto-5′-nucleotide pyrophosphatase/phosphodiesterase 1 (NPP1), a cell surface protein that catalyzes the hydrolysis of ATP to AMP and extracellular inorganic pyrophosphate (PPi; Rutsch et al., 2001; Goding et al., 2003). PPi potently inhibits hydroxyapatite crystal deposition and growth and regulates chondrogenesis, collagen I expression and synthesis, and other cell differentiation processes (Bollen et al., 2006; Goding et al., 2003).

PXE AND ABCG6 MUTATIONS

Pseudoxanthoma elasticum (PXE; OMIM 264800) is a hereditary, autosomal recessive, multisystemic disease characterized by ectopic mineralization and fragmentation of elastic fibers of soft connective tissues such as the skin, the retina, and the arterial blood vessels. The clinical manifestations of classic PXE center on the skin, the eyes, and the cardiovascular system. The primary cutaneous lesions are small, yellowish papules on the neck and in large flexural areas, and these lesions progressively coalesce to form larger plaques, and skin folding occasionally develops. The eyes are frequently involved by calcification of Bruch’s membrane leading to angiod streaks, and bleeding from the choroidal vessels can result in loss of visual acuity and, occasionally, in central blindness. The cardiovascular manifestations derive from mineralization of arterial blood vessels, and include gastrointestinal bleeding, intermittent claudication, hypertension, and sometimes early myocardial infarcts. Additionally, PXE can manifest with gastrointestinal hemorrhage and abnormal tissue mineralization in different organs, including the liver, kidneys, spleen, breast, and testes (Li et al., 2009; Plomp et al., 2010). Although dermatological signs are common, the main burden of PXE results from the complications in the visual and cardiovascular systems (Hu et al., 2003). Cutaneous and eye involvement usually occurs in adolescence, but may appear earlier in childhood. Cardiovascular complications usually develop later, in mid-adulthood (Nasouri et al., 2009). The prevalence of PXE is estimated to 1/25,000 to 1/75,000 in the general population (Chassaing et al., 2005; Li et al., 2009). Mutations in the ABCG6 (ATP-binding cassette subfamily C number 6) gene are demonstrated in about 66–97% of patients who are genotyped (Bergen et al., 2000; Le Saux et al., 2000, 2001; Miksch et al., 2005; Chassaing et al., 2007; Vanakker et al., 2008). The ABCG6-transported substrate or substrates, which mediate arterial calcification and other phenotypic changes of PXE, are not known, and hepatic abnormalities that have effects on calcification-regulating plasma proteins such as fetuin have been suggested to at least partially mediate the pathogenesis of PXE (Hendig et al., 2006).

Generalized arterial calcification of infancy and PXE have been considered to be two distinct entities in the past and have been...
and GACI. We hypothesized that GACI could be independent of mutation in The patient was also found to harbor a homozygous missense thomatous lesions of the neck, inguinal folds, and lower abdomen. A relatively mild form of GACI developed PXE with pseudoxan-
et al., 2012). Most recently, one additional 2-year-old patient with three living family members (Le Boulanger et al., 2010). However, no ENPP1 mutations were found in the three living family members (Le Boulanger et al., 2010).

This case was the first one suggesting a correlation between PXE and GACI. We hypothesized that GACI could be independent of ENPP1, but related to ARCO6 mutations and that on the other hand PXE could be related to ENPP1 mutations.

PATIENTS WITH GACI CARRY MUTATIONS IN ARCO6
Based on this case of GACI and PXE in one family with ARCO6 mutations, we sequenced the ARCO6 gene in 30 patients with a typical GACI phenotype but without disease-causing ENPP1 mutations. In 14 of these patients, we detected pathogenic mutations in ARCO6 (biallelic mutations in eight patients, monoallelic mutations in six patients). This study showed that biallelic mutations in the ARCO6 gene account for a substantial number of typical GACI cases (Nitschke et al., 2012). The fact that even monoallelic mutations in ARCO6 were associated with the severe phenotype of GACI cannot fully be explained on the basis of autosomal recessive inheritance. However, mutations of other disease-associated genes have not been ruled out so far.

PATIENTS WITH GACI AND PXE CARRY MUTATIONS IN ENPP1
Three of our GACI patients, who showed extensive calcifications of the large- and medium-sized arteries, arterial stenoses, and periarticular calcifications in infancy, carried biallelic ENPP1 mutations. These patients developed clinical features of PXE in childhood between 5 and 8 years of age. The patients showed angiod streaks and typical pseudoxanthomatous skin lesions (Nitschke et al., 2012). Most recently, one additional 2-year-old patient with a relatively mild form of GACI developed PXE with pseudoxan-
thomatous lesions of the neck, inguinal folds, and lower abdomen. The patient was also found to harbor a homozygous missense mutation in ENPP1 (Li et al., 2012).

GENOCOPY AND PHENOCOPY IN GACI AND PXE
GACI and PXE have been considered to be two distinct enti-
ties in the past and have been primarily linked to ENPP1 and ARCO6, respectively. But based on the overlap of geno-
type and phenotype of GACI and PXE, both entities appear to reflect two ends of a clinical spectrum of ectopic calcification and other organ pathologies, rather than two distinct disorders (Figure 1). It was shown, that biallelic mutations in ARCO6 account for a significant number of typical GACI cases, which involve widespread arterial calcifications, arterial stenoses, periarticular calcifications, and hypophosphatemic rickets. ARCO6 mutations can be associated with a much more severe pheno-
type, including death in infancy from myocardial infarction, than was previously known. We conclude that the phenotypic spectrum of diseases associated with ARCO6 mutations is much broader than was previously assumed. In fact, the infantile phenotype of patients carrying ARCO6 mutations can be indistin-
guishable from the phenotype associated with ENPP1 mutations. The fact that the same ARCO6 mutations can cause the severe GACI phenotype associated with death in early infancy and the
relatively mild phenotype of PXE warrants further explanation. Because of the difficulty of charting a clear pattern of inheritance to phenotype, it is likely that mutations in other disease-associated genes may play a role here.

Up to date, four patients who presented with GACI and carried biologic ENPP1 mutations developed the clinical manifestation of PXE in childhood. Symptoms included angiod streaks and histologically proven calcifications of elastic skin fibers. Thus, given the poor prognosis of severe GACI, affected patients might die of the cardiovascular complications of the disease before they develop typical signs of PXE. This might be the reason that no previous case of GACI has been described in the PXE literature. Also, many PXE characteristics, including angiod streaks of the retina and peau d’orange skin lesions might frequently be overlooked in the clinical examinations of GACI patients. Hence, the true number of patients carrying ENPP1 mutations and showing PXE lesions might be higher. In summary, these findings show that mutations in different genes ENPP1 and ARCO6 can lead to similar pathophysiological consequences and that GACI and PXE do not simply represent two distinct disorders. They rather represent a spectrum of different peculiarities of ectopic calcification. It can therefore be hypothesized that the pathophysiology of ENPP1 and ARCO6 related disorders is based on common downstream mechanisms.

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