MEGALENCEPHALY CAPILLARY MALFORMATION (MCAP)

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INTRODUCTION Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) is characterized by cutaneous capillary malformation occurring in association with megalencephaly with a tendency to progressive enlargement, cortical brain malformations, most distinctively polymicrogyria, abnormalities of somatic growth with body and brain asymmetry, developmental delay, and typical face with full cheeks, frontal bossing, and nevus flammeus of the nose and/or philtrum and upper lip. Some cases of MCAP have been found to have somatic mutations in the PIK3CA gene on chromosome 3q26 with evidence of mostly postzygotic mosaicism [Riviere et al., 2012]. All reported cases occurred sporadically. Increased paternal age was noted. Significant overlap has been observed with megalencephaly polymicrogyria-polydactyly hydrocephalus (MPPH; see this term); in fact MCAP and MPPH result from mutations in the same pathway, with a central role of PI3K-AKT signaling in vascular, limb and brain development.
We present 3 unrelated patients with MCAP and we underline the evolution of the phenotype over time.
CLINICAL CASES 1st PATIENT This female infant is the first child born by vertex delivery at 35 weeks gestation to healthy non-consanguineous parents. The pregnancy was unremarkable with no known exposures to potential teratogens. Birth weight was 4.240 g (>99th centile) and length of 52 cm (>98th centile). She had hypoglycaemia. On examination in the newborn period she showed general hypotonia and a congenital generalised “marbled” or “mottled” skin appearance, prevailing on the face and right arm and exaggerated by crying. In addition there was a nevus flammeus of the philtrum, full cheeks and bilateral 2/3 syndactyly of the toes. . She had mild developmental delay, with particular involvement of expressive language, and she walked at 24 months. At the age of 10 years and 7 months her height was 146 cm (75th centile), the weight was 50 kg (>97th centile) and the head circumference 58.5 cm (>+2SD). In addition to the features mentioned above she had hypertelorism, epicanthic folds and body asymmetry with left hemihypertrophy .
Chromosome analysis of cultured lymphocytes at 450 band resolution and skin fibroblasts were normal and did not reveal any chromosomal mosaicism. Ultrasound of the abdomen did not show any evidence of haemangiomata of the abdominal viscera. Left kidney length was 8.2 cm, right kidney 7.7 cm. An x-ray of the lower limbs showed the right leg was shorter than the left by 0.9 cm. Computerised tomography and MRI scan of the head showed left hemimegalencephaly, mild ventriculomegaly, periventricular increased signal of white matter and a Chiari type I malformation. Doppler of the legs was negative for arteriovenous fistulae. Electrocardiogram and fundoscopy were normal. Genetic investigations (Seattle Children Research Institute): *PIK3CA* analysis: mutation p.E970Kmos in exon 20 in saliva The mutation is de novo and mosaic(only present in saliva 27% mutated allele and undetectable by Sanger in the blood) Ongoing: deep sequencing in the blood to see if the mutation could be present at low level of mosaicism(less then 10%).- Next Gen Sequencin technology. There is another patient with the same mutation, found in LB cell line (not published).
2nd PATIENT This child is the first male born at 40 weeks gestation to healthy non-consanguineous parents. The pregnancy was unremarkable. He was born by vertex delivery, with a birth weight of 3.700 g (75th centile) and a length of 52 cm (75th centile). On examination at the age of 5 years his head circumference was 56 cm (>+2SD), weight 18.6 kg (50th centile) and height 103 cm (10th centile). There was generalised mottling of the skin, especially apparent on the face, trunk, abdomen, hands, feet and right arm. He had a nevus flammeus of the philtrum, the occiput

and over the back. There was, in addition, a cavernous haemangioma of the back and body asymmetry with left hemihypertrophy involving the face, and foot. He had minimal cutaneous syndactyly of the 2nd and 3rd toes bilaterally. He had normal psychomotor development. Chromosome analysis of cultured lymphocytes at 550 band resolution was normal. Ultrasound of the abdomen was also normal, as was a sacral spine x-ray and Doppler examination of the legs. Echocardiogram and fundoscopy were normal. MRI of the head showed left hemimegalencephaly and periventricular increased signal of white matter
Genetic investigations (Seattle Children Research Institute): *PIK3CA* analysis in saliva, buccal swab and blood: ongoing
3rd PATIENT This female is the first child born by cesaren delivery at 34 weeks gestation to healthy non-consanguineous parents. The pregnancy was unremarkable with no known exposures to potential teratogens. Chromosome analysis of cultured amniocyte were normal. Birth weight was 2.900 g (90th-97th centile) She had mild developmental delay, with particular involvement of expressive language, and she walked at 24 months. She had hydrocephaly (operated at the age of 12 months) On examination at the age of 6 years and 1 month she had a a congenital generalised "marbled" or "mottled" skin appearance, prevailing on the face and left arm and exaggerated by crying. In addition there was asimmetry of the face, hypertelorism, a nevus flammeus of the philtrum, upper lip and glabella, gengival hypertrophy, full cheeks, right 2/3 syndactyly of the toes. In addition to the features mentioned above she had body asymmetry with left hemihypertrophy and scoliosis. At the age of 6 years and 1 month her height was 124 cm (97th centile), the weight was 28 kg (>97th centile) and the head circumference 60.5 cm (>>+2SD). Ultrasound of the abdomen did not show any evidence of haemangiomata of the abdominal viscera. Computerised tomography and MRI scan of the head showed left hemimegalencephaly, ventriculomegaly, periventricular increased signal of white matter and a Chiari type I malformation. Laringoscopy demonstrated epiglottis asymmetry Echocardiography showed a atrial septal defect. Genetic investigations (Seattle Children Research Institute): *PIK3CA* analysis in saliva, buccal swab and blood: ongoing
CONCLUSIONS: The clinical diagnosis of MCAP is possible at birth and may be supported by MRI brain findings of a CNS phenotype and by molecular analysis of the PIK3CA gene [blood/saliva/buccal swab]. Variable levels of mosaicism depending on the tissue tested have been observed.
Management requires a multidisciplinary approach (involving neurology, ophthalmology, cardiology, orthopedics, ultrasound and Doppler ultrasound, radiology, audiometrics, physiotherapy, psychology and dermatology)

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