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A case of Incontinentia Pigmenti associated with congenital absence of portal vein system and nodular regenerative hyperplasia

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Dear Editor, Congenital absence of portal vein system (CAPVS) is a rare condition in which portal perfusion is bypassed by portosystemic shunt leading to the development of portal hypertension (PH) or porto-systemic encephalopathy (PSE) [1]. Visceral anomalies and liver cancer can be associated with CAPVS[1].Thanks to the advances in imaging, the number of CAPVS cases detected has increased. Incontinentia Pigmenti (IP) (OMIM #308300) also represents a rare condition, characterized by skin, teeth, hair, nails, eyes and central nervous system alterations, due to mutations of *NEMO/IKBKG* gene.[2]

We report on the first case of IP associated with CAPVS and nodular regenerative hyperplasia (NRH) of the liver, in a patient with facial dysmorphisms and speech delay. Although rare, this finding may support the role of *NEMO* in liver homeostasis.

At the age of 45 days, a diagnosis of IP was suspected based on the presence of erythematous vesicular skin lesions along Blaschko lines all over the body, consistently with a stage one. The diagnosis was based on updated IP diagnostic criteria[3] and confirmed by the molecular analysis of *NEMO*[4], revealing a deletion of exons 4-10, not present in the parents. Skin biopsy showed marked epidermal spongiosis, dyskeratotic keratinocytes, outbreaks of intra-epidermal keratinization, eosinophilic infiltrate in the papillary dermis. At 10 years of age, clinical examination showed brown hyperpigmented streak lesions on the trunk and the limbs (Fig.1A-1B), matching a stage three; she also had a history of speech delay while no alterations of the teeth, eyes, hair and nails were identified. An array-CGH was performed due to the detection in the patient and in her brother, not carrying *NEMO* alterations, of speech delay and facial dysmorfisms as prominent forehead and depressed nasal root. It showed the presence of a duplication of the region 11q25, including the Neurotrimin (*NTM*) gene, inherited from the asymptomatic father, a *de novo* deletion of the region 14q32.33, including a part of the immunoglobulin heavy locus (*IGH*) gene and of the region 15q11.2, including the Non Imprinted In Prader Willi/Angelman1 (*NIPA1*) and *NIPA2* genes, inherited from the asymptomatic mother and also identified in the brother. An abdominal ultrasound revealed the presence of a hyperechogenic liver lesion, suggestive of hepatic hemangioma. A MRI revealed the presence of liver enlargement and multiple hepatic lesions, hyperintense on T1-weighted images and with low T2 signal, in the right lobe, interpreted as NRH. The contrast medium revealed the absence of the portal vein system, the presence of a large extrahepatic shunt originating from the superior mesenteric vein and an ectasia of the inferior cava vein (ICV). To define its morphology, an Angio-CT scan was performed. At the portal confluence, a small vessel was identified: its diameter progressively reduced approaching the ICV and it was not possible to characterize the site of connection between it and the ICV. The

superior and the inferior mesenteric veins were ectasic and drained to systemic circulation through a large group of collateral circles, flowing into the haemorrhoidal plexus and the internal iliac vein (Fig.1 C-1D-1E-1F-1G-1H). Considering that liver function was only slightly impaired, no surgical procedure was recommended. However, an intensive follow-up was scheduled.

We reported on the first case of IP associated with NRH and CAPVS. A role for *NEMO* in vascular and hepatic homeostasis has been hypothesized.[5,6] Hepatic adenomatosis and hepatoportal sclerosis, due to changes in hepatic vascularisation, have been previously described in one IP patient.[5] Moreover, mice lacking *NEMO* in liver cells develop liver inflammation, fibrosis and hepatocellular carcinoma and male *NEMO/IKKγ* knockout mouse die in utero because of liver apoptosis.[6,] However, since this association is extremely rare, never reported in any of large cohorts[7] of IP patients, it is not possible to define if *NEMO* deficiency contributed to the pathogenesis of the CAVPS. Nevertheless, considering that CAVPS may be asymptomatic and that, if undiagnosed, it can lead to PH or PSE, hepatic ultrasonography should be performed at least once during the follow-up of IP. It should be noted that our patient carried other genetic alterations. No clinical features linked with the 11q25 duplication were identified. However, she also carried a de novo 14q32.33 deletion that has been associated with dysmorphic features[8], intellectual disability[8] and cardiac defects. Moreover, the 15q11.2 deletion, identified in the asymptomatic mother and in the brother, has been associated with developmental delay and facial dysmorphisms. It has been also occasionally associated with congenital heart defect, genital abnormalities, cataracts and hearing impairment. In this context, we cannot exclude that other genomic alterations may have been involved in the pathogenesis of the CAPVS.

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