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LETTER TO THE EDITORS

Nicolaides–Baraitser syndrome: defining a phenotype

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Dear Sirs,

We report here on an adult patient affected by Nicolaides–Baraitser syndrome (NCBRS, OMIM #601358) who also presented with multiple cerebral cavernous malformations and insulin resistance and we discuss the relevance of these findings for NCBRS patients.

NCBRS is an increasingly recognized cause of intellectual disability linked to a defective epigenetic mechanism [1, 2]. A typical picture of NCBRS is emerging after the recent identification of the responsible gene *SMARCA2* [3]. *SMARCA2* encodes a subunit of the switch/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex which is involved in gene transcription, cell differentiation, and DNA repair [3]. Beside intellectual delay, seizures, facial coarsening, short stature, microcephaly, sparse scalp hair, and prominent interphalangeal joints seem to be cardinal features [4]. Nevertheless, NCBRS phenotype delineation is still based on a limited number of reported cases. This makes difficult the attribution of uncommon features as syndromic or coincidental to the disease. Moreover, somatic and germline mutations of the SWI/SFN complex have been associated with tumor suppression, raising the question whether patients with intellectual disability harboring SWI/SNF mutations might have increased risk of developing neoplasias [5]. A lack of reported cancers in these patients may be due to the fact that many of them are juveniles that have been not followed after their childhood [5].

Mari et al. described recently the clinical and molecular details of a cohort of Italian patients [2]. Patient 2 in their report is a 35 years old woman with a heterozygous c.2554G>A mutation in exon 18. Her clinical picture largely overlapped those of other NBS patients: she presented with cognitive delay and limited speech, epilepsy, microcephaly, short stature, decreased subcutaneous fat, coarse facial features, sparse scalp hair and dense eyebrows, and facial and dorsal hypertrichosis. Further investigations, however, led to two additional interesting findings. First, a brain MRI showed cerebral atrophy with frontal lobe hypoplasia and multiple cerebral cavernous malformations (CCMs). Both the proband and her mother, who also suffered from headache and CCMs, were found to harbor a c.2012 insCAAC in the exon 17 of *KRIT1* (CCM1). While the two genetic diseases were likely inherited independently by the proband, they might hypothetically have reciprocally influenced the proband's phenotype. A two-hit mechanism (germline and somatic) leading to the inactivation of both alleles within affected cells has been proposed for the genesis of CCMs and other vascular malformations [6]. In the two-hit model, a germline mutation is inherited in one allele and lesions occur in cells in which also the wild-type allele is inactivated [7]. We wonder, then, if *SMARCA2* mutations might favor the development of vascular malformations by contributing to inactivate the spared allele at a somatic level. Indeed, *SMARCA2* mutations associated with NCBRS generate a

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structurally undamaged but dysfunctional SWI/SNF complex that interacts properly with chromatin but is functionally inactive, altering both the normal induction and repression of genes [3]. Interestingly, in the small NCBRS population described so far, three patients presented vascular malformations [8, 9].

Furthermore, our patient showed hyperinsulinemia with usually normal glycemic values. The family reported that occasional episodes of aggression occurred in correspondence with moderate hyperglycemia. Occasional aggressive periods in otherwise happy and friendly patients are an unexplained feature of NCBRS [4]. Moreover, insulin resistance syndromes are often associated with hirsutism, poor subcutaneous adipose tissue, coarse facial features, dental and nail dysplasia, and short stature which also are typical features of NCBRS [8, 10].

A critical report of uncommon findings in NCBRS might help to better delineate its phenotype and might suggest broader investigations in other NCBRS patients.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard Written informed consent was obtained; the study complied with the Declaration of Helsinki.

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