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Neonatal hypocalcemia revealing a malignant osteopetrosis.

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BACKGROUND

A one-month girl was referred to our unit for hypocalcemia. She was the first child of healthy non-consanguineous parents. Her family history was unremarkable except a miscarriage in the mother and oligoasthenospermia in the father that justified a medically assisted reproduction. She was born eutrophic at term after a pregnancy marked by a moderate gestational diabetes. On day 3, a routine neonatal screening revealed a severe asymptomatic hypocalcemia (total calcium: 1.6 mmol/l). According to neonatal unit protocol, an oral treatment with calcium gluconate 200 mg/d and calcitriol 10 drops/d was started.

METHODS AND NVESTIGATIONS

Laboratory investigations performed on day 7 (see Table) showed persistent hypocalcemia, phosphatemia at lower limit, normal alkaline phosphatase levels and low urinary calcium/creatinine ratio. Serum PTH levels were high, consistent with secondary hyperparathyroidism, and were associated with normal 25-hydroxyvitamin D (25OHD) level, and very high 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) level. CBC was normal.

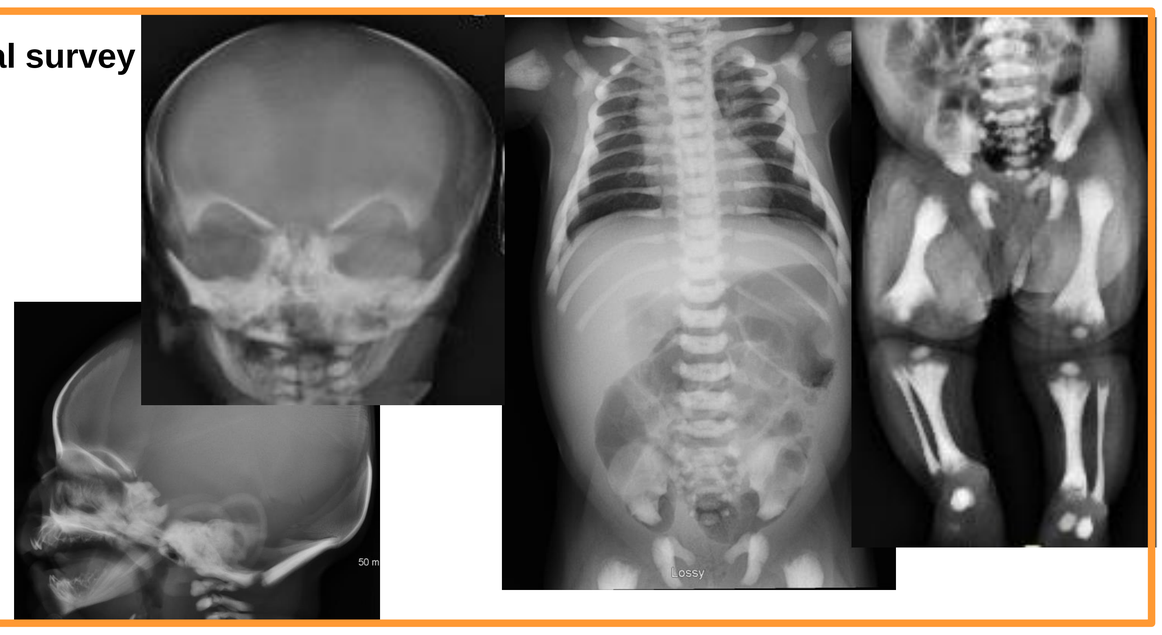
Skeletal survey revealed the association of rickets with metaphyseal impairment and focused osteocondensation lesions on skull basis, limbs and vertebrae, suggestive of osteopetrosis.

The Genetic analysis found combined heterozygous mutation in the TCIRG1 (T-Cell immune regulator 1) gene, confirming a malignant neonatal osteopetrosis. The mutations were inherited from each parent: c.1682delinsTT, p.(Gly561Valfs*109) from the father and c.2383_2384delTC, p.(Ala796Leufs*34) from the mother.

	Day 7		Month 1		Month 1,5	
	Patient	Ref range	Patient	Ref range	Patient	Ref range
Ca (mmol/l)	1,89	2-2,6	2,21	2,25-2,75	2,4	2,25-2,75
Ph (mmol/l)	1,4	1,4-2,5	1,14	1,1-1,95	1,07	1,1-1,95
PAL (UI/l)	223	83-248	477	122-465	817	129-417
Mg (mmol/l)			0,76	0,65-0,91	0,96	0,65-0,91
PTH (pg/ml)	429	15-65	527	15-65	285	15-65
25OHD (ng/ml)	30	20-80	33	20-80		
1,25(OH)2 D (pg/ml)	342	18-60	346	18-60	>371	18-60
HCO3- (mmol/l)	20	18-27	20	18-27	20	18-27
Ca/Cr urine sample	0,15		0		0	

Table- Laboratory values according to age

Skeletal survey



EVOLUTION AND MANAGEMENT

Given the high levels of $1,25(OH)_2D$, calcitriol treatment was stopped and substituted by colecalciferol.
On day 45, asthenia, pallor, and purpuric lesions were noted without hepatosplanomegalia. CBC confirmed bicytopenia with anemia (9.2 g/dl), thrombocytopenia (17 G/l) and myelemia (3%). Moreover, she presented eye tracking defect. Cerebral TDM found a homogenous sclerosis on the optic canal, evoking optic nerve compression. Ophtalmic evaluation revealed optic atrophy and bilateral visual defect.

TCIRG1 codes for a subunit of a proton pump expressed on the ruffled border of osteoclasts membrane. It causes osteoclast dysfunction, leading to failure of bone resorption. As oscteoclasts precursors belong to monocyte lineage, stem cell transplantation has been shown to be an effective treatment and was performed in our patient at 3 months of age [1].

CONCLUSION

Malignant osteopetrosis is a rare bone disease (estimated incidence of 1/200,000 live births) due to impaired osteoclast activity or development, with defective resorption of immature bone. Paradoxal hypocalcemia can be the first sign of the disease as osteoclasts are unable to release calcium from bone [2]. Patients presenting TCIRG1 mutations may have co-occurrence of osteopetrosis and rickets on the radiographs, described as osteopetrorickets, as in our case [3]. Without stem cell transplantation, the evolution can be fatal. Early diagnosis is required to perform stem cell transplant before neurosensorial impairment.

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