Subcutaneous fat necrosis of the newborn: A systematic review of the literature

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Background

Subcutaneous fat necrosis of the newborn (SCFN) is a rare disease occurring in the first days of life [1]. Characteristically the infants show hard nodules in subcutaneous tissue, purple or erythematous in color and appear on the upper back, cheeks, buttocks and limbs. In most cases SCFN is a self-limiting disease, as the nodules disappear in up to 6 months. A severe complication associated with SCFN is the hypercalcemia. Pathophysiological mechanisms causing SCFN or associated hypercalcemia are not fully understood [2].

Methods

A systematic literature research following the PRISMA-Statement including the six biggest databases for medical research has been used to identify all published case reports of SCFN. N=206 publications have been identified containing n=320 case. All cases have been classified into four subgroups (depending on reported serum calcium level): hypercalcemia, normocalcemia, hypocalcemia or no serum calcium level was reported. Reported maternal factors, birth characteristics, diagnosis and therapy of the SCFN as well as long-term observations have been extracted from the identified publications.

Results

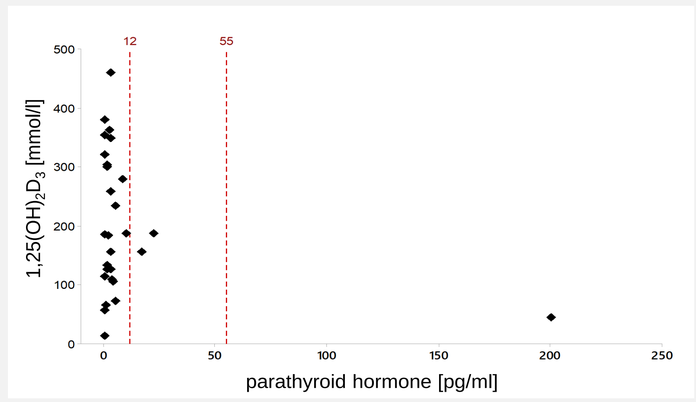
- N=320 case reports
- number of cases per serum calcium level group:
  - normocalcemia: N=52
  - hypercalcemia: N=146
  - hypocalcemia: N=9
  - no information available: N=113
- identified risk factors for SCFN (Table 1):
  - gestational diabetes and maternal hypertension
  - high birth weight and longer duration of pregnancy
  - complications during birth associated with peripheral hypoxia
- histological findings showed a granulomatous inflammation in 98% of the cases
- hypercalcemia seems to be independent from parathyroid hormone levels in affected newborns (Figure 1)
- pathophysiological mechanism of SCFN (Figure 2):
  - cellular damage due to hypoxia in peripheral tissue
  - granulomatous inflammation is related to PTH-independent hypercalcemia

Table 1: Maternal risk factors, birth characteristics, birth complications and therapeutics of the SCFN reported in the n=320 cases in total as well as separated by the groups of serum calcium levels (normocalcemia, hypercalcemia, hypocalcemia or no information about serum calcium level reported)

	serum calcium levels (divided into categories)				
	total n (%)	**normocalcemia n (%)**	**hypercalcemia n (%)**	**hypocalcemia n (%)**	**no information about serum-calcium n (%)**
maternal risk factors	**62**	**14**	**21**	**1**	**26**
gestational diabetes	24 (38.7)	3 (21.4)	10 (47.6)	1 (100)	10 (38.5)
hypertension/preeclampsia	19 (30.6)	5 (35.7)	4 (19.0)	0 (0)	10 (38.5)
diabetes mellitus typ1	6 (9.7)	1 (7.1)	3 (14.3)	0 (0)	2 (7.7)
drugs	7 (11.3)	3 (21.4)	2 (9.5)	0 (0)	2 (7.7)
smoking	6 (9.7)	2 (14.3)	2 (9.5)	0 (0)	2 (7.7)
birth characteristics					
pregnancy duration [weeks] (mean ± SD)	39.3 (±2.6)	38.3 (±2.1)	39.7(±2.1)	41 (±0)	38,3 (±3)
Birth weight [g] (mean ± SD)	3606 (± 759)	3232 (±937)	3873 (±650)	3975 (±763)	3638 (±560)
birth complications in total	**442**	**65**	**231**	**15**	**126**
compatible with peripheral hypoxemia[a]	256 (57.9)	41 (63.1)	128 (55.2)	9 (60.0)	78 (61.9)
meconium aspiration	48 (10.9)	3 (4.6)	35 (15.1)	0 (0)	10 (7.9)
meconium in amniotic fluid	41 (9.3)	6 (9.2)	18 (7.8)	3 (20.0)	14 (11.1)
hypoglycemia	41 (9.3)	4 (6.2)	21 (9.1)	1 (6.7)	15 (11.9)
cerebral seizures	27 (6.1)	4 (6.2)	18 (7.8)	0 (0)	5 (4.0)
tachypnoea	14 (3.2)	2 (3.1)	5 (2.2)	2 (13.3)	5 (4.0)
acute renal failure	10 (2.3)	2 (3.1)	7 (3.0)	0 (0)	1 (0.8)
dystocia	5 (1.1)	3 (4.6)	0 (0)	1 (6.7)	1 (0.8)
therapeutic measures to treat birth complications	**256**	**53**	**122**	**8**	**73**
compatible with peripheral hypoxemia [b]	172 (67.2)	37 (69.9)	84 (68.9)	4 (50.0)	47 (64.4)
others (drugs, coma, phototherapy, reduction of intracranial pressure)	84 (32.8)	26 (49.0)	38 (31.1)	4 (50.0)	26 (35.6)

[a] including asphyxia, respiratory weakness, hypoxic-ischemic encephalopathy, hypoxemia, sepsis or infection, peripheral cyanosis, hypotension, anemia, fetal distress and bradycardia, [b] Including intubation/ ventilation, therapeutic hypothermia and reanimation; SD: standard deviation

Figure 1: Correlation between serum-1,25$(OH)_2D_3$ (mmol/l) and parathyroid hormone levels (pg/ml) in patients with SCFN (red dotted lines represent the reference range for parathyroid hormone levels in newborns)



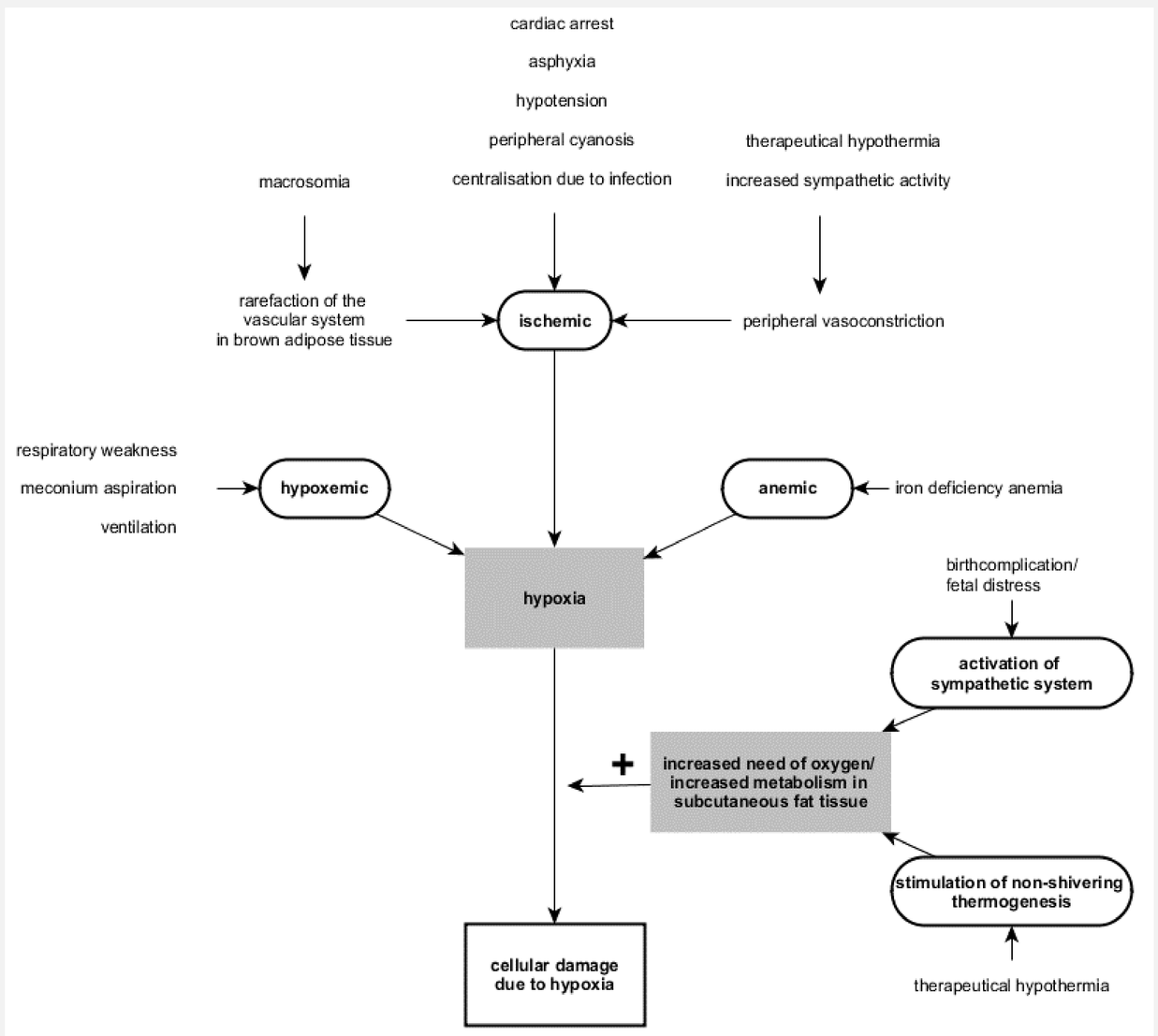


Figure 2: Overview of possible reasons for hypoxia and for the increased need of oxygen or the increased necrosis of subcutaneous fat leading to a cellular damage in the subcutaneous fat tissue

Conclusion

We identified that maternal gestational diabetes and hypertension, higher birth weight, a longer pregnancy duration as well as complications during birth are associated with hypoxia and are risk factors for SCFN. The majority of patients with SCFN develop a hypercalcemia. Practically active pediatricians should examine the skin of a newborn with these risk factors carefully to prevent the possible complication of hypercalcemia of SCFN. Hypoxic cell damage is thought to be the cause of subcutaneous fat necrosis in patients with SCFN. It is assumed that granulomatous inflammation in patients with SCFN causes a lack of the negative feedback mechanism of the enzyme 1-α hydroxylase which is independent from parathyroid hormone levels. This missing negative feedback mechanism leads to an overproduction of vitamin D, causing an increased absorption of calcium via the intestine and consequently results in a hypercalcemia.

References

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