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CLINICAL CASE REPORT

Refeeding syndrome in children with different clinical aetiology

J Lenicek Krleza[1], Z Misak[2,4], O Jadresin[2,4] and I Skaric[3,4]

Refeeding syndrome (RFS) is a well-described state of the series of metabolic and biochemical changes that can occur during the feeding of malnourished persons. The shifts in fluids and electrolytes can lead to complications during artificial feeding, which if not recognised and untreated can lead to death. Although the physiology and pathophysiology of RFS is well known, the circumstances under which the RFS appears, clinical manifestations and management of these patients are less clear. There are few published studies describing the occurrence of RFS in children. We describe two cases of RFS in children. The first case is a boy with unrecognised coeliac disease and second case is a girl with cerebral palsy. In both cases, the RFS has developed without clinical symptoms and it was shown only through laboratory findings. Electrolyte disturbances have been successfully corrected and treatment of the underlying disease continued.

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INTRODUCTION

Refeeding syndrome (RFS) describes the biochemical changes, clinical manifestations and complications that can occur as a consequence of feeding a malnourished catabolic individual.[1] It is defined as severe (and potentially fatal), electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding, whether orally, enterally or parenterally. The hallmark findings are fluid and electrolyte dysregulation, including hypophosphataemia, hypomagnesaemia, hypokalemia, abnormalities in glucose metabolism, vitamin (importantly thiamine) and trace element deficiencies.[2,3] During realimentation, insulin stimulates the entry of glucose, phosphorus, magnesium and potassium into the cells. All these minerals and cofactors (as thiamine) are needed for rapid glycogen, protein and fat synthesis in refeeding. Symptoms of RFS are variable, unpredictable and reflect the type and severity of underlined biochemical abnormality. The spectrum of presentation may range from nausea, vomiting to respiratory insufficiency, cardiac failure, hypotension, arrhythmias, coma and death.[1,2,4] Therefore, prevention and early identification of patients at risk, monitoring during refeeding and appropriate feeding regimen are the keys to successful treatment.[1] Refeeding should be started at no more than 50% of energy requirements in patients who have not eaten little or nothing for >5 days. For patients with high risk (chronically undernourished, little or no nutritional intake for >10 days) nutritional repletion should started be even more slowly (max. 0.042 MJ/kg/day (10 kcal/kg/day or even less) and slowly increased to full needs over 4–7 days.[7] Although, most of the published case reports refer to adult patients, there are some recent reports on RFS occurring in children with coeliac and Crohn's disease.[5,6] We present two pediatric cases of RFS, one in a child with coeliac disease and the other one in child with cerebral palsy.

CASE 1

At admission to our hospital, a boy at the age of 8 years was listless and emaciated with the 6-month history of weight loss, diarrhoea and vomiting. On examination, he had pallor and psoriatic skin lesions on the extremities. Due to metabolic acidosis, dehydration and electrolyte disarrangement, he received intravenous fluids and enteral nutrition with elemental formula that were gradually introduced. Although he improved clinically, after 5 days, he developed hypophosphataemia reflecting development of RFS. At this point, phosphorus was replaced intravenously for 3 days. Gradually, hypophosphataemia got corrected and stayed within the normal range after the desired and adequate oral caloric intake was achieved. Meanwhile, the diagnosis of coeliac disease was confirmed based on positive tissue transglutaminase antibody and total villous atrophy on duodenal biopsy. The flow of treatment and laboratory test results with basic data are shown in Table 1.

CASE 2

At the admission, a 10-year-old girl with cerebral palsy and haemathemesis was pale, grossly emaciated and undernourished. Immediately after the initial laboratory investigation, she received packed red blood cell transfusion. Additionally in view of prior poor oral intake and diarrhoea, she was given partial parenteral nutrition together with enteral nutrition by nasogastric tube. During the first day of feeding, her serum phosphate, magnesium, calcium and potassium dropped reflecting RFS. Supplements of phosphorous, potassium and magnesium were commenced and the electrolyte concentrations were normalised gradually. Enteral nutrition was progressively increased while parenteral nutrition was decreased and finally stopped after 8 days and the girl continued to gain weight. The flow of treatment and laboratory test results with basic data are shown in Table 2.

[1]Department of Laboratory Diagnostics, Children's Hospital Zagreb, Zagreb, Croatia; [2]Department of Pediatrics, Children's Hospital Zagreb, Referral Center of Pediatric Gastroenterology and Nutrition, Zagreb, Croatia and [3]Intensive Care Unit, Department of Anesthesiology, Children's Hospital Zagreb, Zagreb, Croatia. Correspondence: Dr J Lenicek Krleza, Department of Laboratory Diagnostics, Children's Hospital Zagreb, Klaiceva 16, Zagreb 10000, Croatia.
E-mail: jlenicek@gmail.com
[4]These authors contributed equally in the clinical segment of this work.
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Table 1. The flow of treatment and laboratory test results with basic data in boy with coeliac disease (Case 1)

Age/gender		8 years, 10 month/boy										
	Weight (kg)/ weight *Z* score	17.1/ − 4.3	21.3 kg (before leaving the hospital)									
	Height (cm)/ height *Z* score	125.5/ − 1.2	Hospital duration: 3 weeks									
	BMI (kg/m^2)/BMI *Z* score	10.9/ − 6.8	28 August until 16 September 2008									
	Status at admission	6-Month history of weight loss, diarrhoea and vomiting, suspected coeliac disease										
	Days in hospital	First day[a]	Second day	Third day	Fourth day	Fifth day[b]	Sixth day	Seventh day	Eighth day	Tenth day	Thirteenth day	Nineteenth day
	Hospital department	Gastro/IUC	ICU	ICU	ICU	ICU/Gastro	Gastro	Gastro	Gastro	Gastro	Gastro	Gastro
Feeding												
Parenteral	Glucose g/TPN kcal	60/200	100/340	100/340	100/340	70/530	100/760	100/760	60/540	60/540	0	0
Enteral	kcal	100	200	240	300	500	800	800	980	980	1600	1600–1800
	Solutions[c]	C	B,D	A, D	A, D	A, D	A, D	A, D	A, D	A, D	D, GFD	D, GFD
Correction of electrolyte	Solutions[c]	E	E	E	E	F	F	F	—	—	—	—
Total caloric intake	kcal	300	540	820	920	1030	1560	1560	1520	1520	1600	1600
	kcal/kg/day	17.5	31	49	54	76	92	92	90	90	94	80–90
Laboratory test results												
Analyte (units)	Reference range											
Glucose (mmol/l)	3.9–5.9	4.0/5.9	4.7	5.5	5.2	5.9	4.2	4.8	4.6	4.7	4.5	4.5
Potassium (mmol/l)	3.6–5.0	2.1	2.9	3.1	3.7	4.3	4.5	5.2	4.3	4.7	4.5	4.1
Sodium (mmol/l)	135–144	137	138	137	137	142	144	139	142	140	138	139
Phosphate (mmol/l)	1.11–1.73	1.07				**0.28**[d]	0.49	0.50	0.74	0.97	1.44	1.72
Calcium (mmol/l)	2.16–2.63	1.82				1.96	1.97	1.93	2.04	2.14	2.10	2.26
Ionised calcium (mmol/l)	1.22–1.37	1.16 1.12	1.11	1.18 1.12								
Magnesium (mmol/l)	0.74–0.97	0.70				0.74	0.72	0.78	0.81	0.80	0.77	0.77
Albumine (g/l)	42–51	28.8				26						
pH (pH units)	7.35–7.45	7.14/7.34	7.39/7.41	7.477.46	7.47	7.49	7.50	7.51	7.49	7.47	7.45	
Hydrogen carbonate (mmol/l)	22–26	12.5/15.5	16.1/18.9	21.1 23.4	24.4	27.6	28.0	31.6	29.3	30.0	26.5	
Base excess (mmol/l)	− 4 do 2	− 16.2/ − 11.7	− 7.9/ − 7.1	− 2.3–1.3	0.0	3.6	4.0	7.8	5.4	6.2	2.4	
Urea (mmol/l)	2.7–6.8	1.0					2.6				4.1	
Creatinine (μmol/l)	46–80	33					29				30	
CRP (mg/l)	0.1–2.8	37.0			3.0	2.0				0.2	0.2	0.2

Abbreviations: BMI, body mass index. [a]First day: Due to the presence of high metabolic acidosis, boy is moved to the intensive care unit (ICU), introduced intravenous rehydration. [b]Fifth day: Severe hypophosphataemia ([d]) - a reflection of refeeding syndrome. [c]Solutions. **A:** Parenteral nutrition (TPN) was composed by two solutions. Solution I: glucose, amino acids, fat, potassium, sodium, calcium, phosphorus, magnesium, water and Solution II: Lipofundin (B. Braun Melsungen AG, Luxemburg), Vitalipid (Fresenius Kabi AG, Germany), Soluvit (Fresenius Kabi AG, Germany). **B:** Parenteral nutrition (glucose, potassium chloride, sodium chloride, calcium chloride, trace elements (Peditrace, Fresenius Kabi AG, Germany), fat (Intralipid, Fresenius Kabi, Sweden), vitamins (Soluvit, Fresenius Kabi AG, Germany), amino acids (Aminoven, Fresenius Kabi AG, Germany). **C:** Enteral nutrition (oral): Pediasure (Abbott Healthcare Pvt Ltd, India). **D:** Enteral nutrition (gluten and lactose free for oral and nasogastric tube feeding): Peptamen (Nestlé HealthCare Nutrition, Switzerland) diluted with water in ratio 1:1 or 1:2). **E:** Intravenous rehydration solution (glucose, potassium and calcium chloride, sodium bicarbonate - separately). **F:** Intravenous solution for the correction of phosphate: glucose and sodium glycerophosphate pentahydrate (Glycophos, Fresenius Kabi AG, Germany). GFD, gluten-free diet.

Table 2. The flow of treatment and laboratory test results with basic data in girl with cerebral palsy (Case 2)

	Age/gender	10 years/girl										
	Weight (kg)/weight *Z* score	11.2/ − 7.9	13.5 kg (before leaving the hospital)									
	Height (cm)/height *Z* score	109/ − 3.4	Hospital duration: 2 weeks									
	BMI (kg/m^2)/BMI *Z* score	9.4/ − 9.5	5 October until 17 October 2011									
	Status at admission	Haemathemesis, long-time poor oral intake, diarrhoea										
	Days in hospital	First day[a]	Second day	Third day	Fourth day	Fifth day[b]	Sixth day	Seventh day	Nineth day	Tenth day	Fourteenth day	Two months later
	Hospital department	Gastro/ICU	ICU/gastro	Gastro	Gastro	Gastro	Gastro	Gastro	Gastro	Gastro	Gastro	Upvisit
Feeding												
Parenteral	Glucose g/TPN kcal	72/340	72/340	60/240	30/170	30/170	25/135	12/100	12/50	0	0	
Enteral	kcal		150	300	400	400	600	850	1100	1200	1200	
	Solutions[c]	A	A, D	A, D	A, D	A, D	A, D	A, D	A, D	D	D	
Correction of electrolyte	Solutions[c]	E	E	E	E	E	E	E	E	—	—	
Total caloric intake	kcal	340	490	540	570	570	735	950	1150	1200	1200	
	kcal/kg/day	30	44	48	51	51	65	85	95	100	100	
Laboratory test results:												
Analyte (units)	Reference range											BW 15 kg
Glucose (mmol/l)	3.9–5.9			6.1				4.3	4.4		4.7	
Potassium (mmol/l)	3.6–5.0			**2.7**[d]	3.0	4.1	4.8	4.7	4.6		4.5	
Sodium (mmol/l)	135–144			139	139	140	138	138	143		137	
Phosphate (mmol/l)	1.11–1.73			**0.68**[e]	0.71	0.80	1.15	1.25			1.59	
Calcium (mmol/l)	2.16–2.63			**2.09**[f]	2.15	2.17	2.26	2.29			2.31	
Ionised calcium (mmol/l)	1.22–1.37			**1.13**[g]	1.17	1.19	1.21	1.26	1.26		1.36	
Magnesium (mmol/l)	0.74–0.97			**0.71**[h]	0.75	0.76	0.79	0.85			0.83	
Albumine (g/l)	42–51			30				31			32	
Red blood cells (RBC) (x10^{12}/l)	4.3–5.5	2.2/2.4	3.5/3.8	3.8		4.0		3.8			4.4	4.9
Haemoglobin (g/l)	121–145	27/28	74/82	81		85		80			105	124
MCV (fl)	76.5–92.1	51/51	69/69	68		70		72			76	79
MCH (pg)	24.3–31.5	12/12	21/22	21.4		21.2		21.1			24	25
MCHC (g/l)	30.4–34.6	239/231	312/318	315		300		295			316	366
Platelets (x10^9/l)	150–450	659/601	555/507	501		500		477			429	323
White blood cells (WBC) (x10^9/l)	5–13	22/23	24/23	15.9		15.3		8.7			9.4	8.8
CRP (mg/l)	0.1–2.8			14.1				5.0			0.5	
pH (pH units)	7.35–7.45			7.495	7.454	7.391	7.428	7.430	7.436		7.409	
Hydrogen-carbonate (mmol/l)	22–26			25	26.1	23.3	24.9	23.4	23.6		24	
Base excess (BE) (mmol/l)	− 4 do 2			0.6	2	-1.1	0.6	-0.9	-0.6		-0.3	
Urea (mmol/l)	2.7–6.8			1.6				2.3			4.1	
Creatinine (μmol/l)	46–80			33				31			30	

Abbreviations: CRP, C-reactive protein; BMI, body mass index; BW, body weight; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume. [a]First day: Severe anaemia treated with transfusion of red cell concentrate in intensive care unit (ICU). Presented haematology parameters are before and after red blood cells transfusion. [b]Third day: hypokalemia ([d]) hypophosphataemia ([e]) hypocalcemia ([f,g]) hypomagnesiemia ([h]) - a reflection of refeeding syndrome. [c]Solutions. **A:** Parenteral nutrition (TPN) was composed by two solutions. Solution I: glucose, amino acids, fat, potassium, sodium, calcium, phosphorus, magnesium, water and Solution II: Lipofundin (B. Braun Melsungen AG, Luxemburg), Vitalipid (Fresenius Kabi AG, Germany), Soluvit (Fresenius Kabi AG, Germany). **D:** Enteral Nutrition (gluten and lactose free for oral and nasogastric tube feeding): Peptamen (Nestlé HealthCare Nutrition, Switzerland) diluted with water in ratio 1:1 or 1:2). **E:** Intravenous rehydration solution (glucose, potassium and calcium chloride, sodium bicarbonate - separately).

DISCUSSION

Starved and malnourished patients are at risk of developing potentially life-threatening RFS, severe metabolic and biochemical changes that may occur when malnourished patients are aggressively fed (orally, enterally or parenterally).[3–5] In this article, we report two patients who developed RFS, one with newly diagnosed coeliac disease and another with cerebral palsy. Both patients were severely malnourished and developed the complication within days of starting feeding (Tables 1 and 2).

The clinical features of RFS result from the electrolyte disturbances (hypophosphataemia, hypokalemia and hypomagnesaemia) and from disturbed body fluid shifts.[6] Initially, RFS may go unrecognised as it is usually asymptomatic[5,6] just like both of our patients were. Our first patients with coeliac disease developed RFS after 5 days despite parenteral and enteral nutrition were introduced gradually. Feeding was started with 17 kcal/kg/day and on the fifth day, when he developed RFS, he received 76 kcal/kg/day. This means that even slower introduction is needed, most probably with 10 kcal/kg/day as suggested by Stanga *et al.*[7] However, our patient did not have any clinical symptoms, unlike coeliac patients in a recently published article, in whom RFS came in differential diagnosis with coeliac crises.[5] RFS may mimic coeliac crisis, however, treatment goals in these two conditions differ considerably (correction of metabolic and electrolyte abnormalities versus steroids). What might help is the sequence of events: coeliac crisis as a presentation and RFS as worsening on gluten-free diet.[5]

Our second patient was chronically undernourished child with cerebral palsy and both parenteral and enteral nutrition were introduced slowly, although at higher rate (30 kcal/kg/day) than suggested in guidelines.[7] However, as this child was at high risk, RFS was suspected early, before any clinical symptoms, and diagnosed based on electrolyte disarrangements. To our knowledge, there are no reports on RFS in children with cerebral palsy.

RFS should be considered as a potential complication during the first week of provision of nutritional support for severely malnourished and it is important to identify and monitor patients at risk in whom baseline serum concentration of electrolytes should be ascertained before initiation of nutritional support.[5,6] According to guidelines for adults published by Stanga *et al.*[7] for patients with high risk (chronically undernourished, little or no nutritional intake for >10 days), nutritional repletion should be started even more slowly (max. 10 kcal/kg/day or even less) and gradually increased to attain optimal energy requirement over 7–10 days. Electrolyte and fluid imbalances should be corrected along with feeding.[5,7]

In conclusion, it is important for clinicians to be aware of RFS and to identify and monitor patients at risk. Although not all malnourished patients who are refed develop RFS, the syndrome can occur in any malnutrition patient regardless of its cause.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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