Protein requirements – are the recommendations too high?

The fetus receives high amounts of amino acids and some carbohydrates, whereas the term newborn infant gets a low protein diet, lots of carbohydrates and, lots of fat. In preterm infants this transition from fetal nutrition to term newborn nutrition happens in the neonatal ICU and actually, we do not know the best nutrition for the preterm infant.

Especially growth in the NICU has been linked to neurodevelopmental outcome in preterm infants. In ELBW infants (< 1,000 g) postnatal growth failure has been documented repeatedly. E.g. Ehrenkranz (1999) has shown that at term equivalent age up to 90% of ELBW infants developed extrauterine growth retardation defined by a weight below the 10th percentile. More recently this data has been reconfirmed (Cole et al., ADC Fet Neo 2014). An important point to take into consideration is, that in term SGA infants it has not been proven that better nutrition improves neurodevelopmental outcome. Therefore, it has been hypothesized that in preterm infants’ outcome improvement by better nutrition or better growth may only be possible early during early time in hospital.

In a retrospective study in ELBW infants more amino acids (AA) given in the first week of life significantly increased mental developmental index at 18 months and the same was true for energy. (Fig. 1).

Is the recommended protein intake too high?

In 2010, the ESPGHAN committee on nutrition recommended a protein intake of 4.0–4.5 g for infants up to 1,000 g and 3.5–4.0 g for infants from 1,000–1,800 g. Protein supply should compensate for a cumulative protein deficit. Some excess of protein had not been shown to be detrimental. Similar recommendations have been published by others as well. The US Life Science Research Office recommended 3.0–4.3 g/kg/d of protein in 2002, and Koletzko B et al. (World Re Nutr Diet, 2014) 3.5–4.5 g/kg/day protein.

Are these recommendations too high? Human milk is our preferred feeding; it is associated with less necrotizing enterocolitis (NEC). There are a very few trials challenging the recent increased enteral protein recommendations. In a systematic review seven RCTs have been found. (Fig. 2) All studies used standard protein fortification for the control group (on average 1 g of protein / 100 ml of human milk).

The majority of studies did not find an effect on weight or on length gain. In a carefully conducted straightforward trial however, Jacques Rigo (JPGEN 2017) used a high protein human milk fortifier in comparison to a standard human milk fortifier and found a significant effect on weight gain. Therefore, in certain settings it is definitely possible to achieve better weight gain with higher protein supplementation. The study by Maas et al. (JAMA Paediatr. 2017) was quite remarkable.

1st The low protein group achieved normal weight gain on day 28.
2nd There was a trend towards better weight gain with lower protein fortification.
More recent data by Christian Fusch may provide an explanation for these observed effects. In a RCT he studied target fortification of human milk and exactly measured the intake of fat, amino acids / protein and carbohydrates and optimized the supplementation by adding as much protein and as much energy as required. The effect was remarkable. At 36 weeks of corrected age growth was adequate with target fortification. However, in the standard fortification group growth was adequate in infants with high protein human milk and there was growth failure in low protein human milk infants (donor milk or low protein mother’s milk). Therefore, the actual human milk protein concentrations may have significantly confounded the results of the previous studies. However, the exact protein concentration has not been measured in most of the trials.

Are the high protein recommendations safe?

To discuss this subject, I would like to highlight three studies:

- The working group of Carnielli V. (Bellagamba, JPGN 2016) studied the effect of an extra gram of protein in infants < 1,250g. No effect on weight gain or neurodevelopmental outcome has been found.
- The large randomized trial (n=1440) by Greet Van den Bergh (Fizev et al., NEJM 2016) studied parenteral nutrition in the PICU setting. In order to optimize nutrient intake, infants were randomized to receive parenteral nutrition in addition to enteral nutrition right from the first day of life or starting after day 7. With early parenteral nutrition there was a trend to more infections and more days in hospital.
- In a subgroup analysis in 209 term newborn PICU infants late parenteral nutrition (starting AA after day 7 – Verbruggen et al., Lancet 2018) increased the probability for live discharge. (Fig. 4) Therefore, we need to be careful with AA in sick PICU term newborns.

This leads back to target fortification which has been studied by Christoph. Fusch. However, target fortification is time consuming and may not be available for every neonatal department. Jacques Rigo was the first who suggested to measure urea or blood urea nitrogen regularly in infants on enteral nutrition and to adjust human milk fortification. If blood urea nitrogen and weight gain are low he suggested to increase protein and energy intake. If urea is high, you may reduce protein intake in infants who grow nicely or you may try to improve the energy intake in infants who do not grow sufficiently.

This approach has only been studied in one randomized controlled trial by Sertac Arsanoglu. The disadvantage is that it requires regular blood sampling.

Conclusions

- VLBWI are frequently undernourished
- Poor nutrition and poor growth are associated with poor neurodevelopment
- AA/protein is not always beneficial
- Be careful in sick neonates with early PN
- Be careful with routine protein recommendations above 4 g/kg/d
- High AA/protein intake may need to be individualized (target fortification or BUN/urea adjustment)