Abstract

Background: An increasing number of families of SMA children are incorporating the amino acid diet into their child's feeding regimens. Characteristics of the diet include high carbohydrates and low fats, with probiotics. However, due to insufficient evidenced based research clinicians are unable to prescribe or endorse. The aim was to assess the tolerability and safety of an adapted version of the traditional amino acid diet (SMAAD) in children with SMA Type I.

Methods: Children with SMA Type 1 were recruited if enterally fed and experiencing at least one gastrointestinal symptom (reflux, vomiting, constipation and/ or diarrhoea). Children were transferred on to an amino acid formula (Neocate® Syneo™- Nutricia) for eight weeks. Primary outcome: Feed tolerance was measured weekly by telephone consultation to monitor reflux, vomiting, stool consistency and frequency.

Results: Fourteen children were recruited, mean age 4.1 years (±1.2 SD), of which 64% were female. Indirect Calorimetry was measured at the start of the study to assess energy requirements and respiratory quotient. The mean resting energy expenditure 51.5kcal/ kg (±7 SD). The most common gastrointestinal complaint prior to switching to SMAAD was constipation, reported in 12 of 14 (85%), of which 10 of the 12 (83%) children required medication to help bowels open daily. After 8 weeks on SMAAD 10 out 12 (83%) children stopped or reduced constipation medication.

Conclusion: Children with SMA Type I who are displaying gastrointestinal symptoms such as constipation and reflux may benefit from an amino acid formula that is fortified with probiotics.

BACKGROUND

Spinal muscular atrophy (SMA) is the most common genetic cause of mortality in infancy, SMA type I is the most severe form of the disease, accounting for approximately 60% of cases.[1] SMA is characterized by degeneration of brainstem and spinal cord motor neurons that lead to progressive muscle weakness and atrophy.[2] These neurological changes result in progressive swallowing, feeding and gastrointestinal complications as well as respiratory failure.[3]

Improvements in standards of care and the advent of new therapeutic approaches have resulted in improvements in survival and functional abilities in these patients, changing the course of the disease.[4, 5] So far, most of the attention has been focused on survival and motor or respiratory outcome.[6, 7] Despite feeding being one of the most important aspects in the care of SMA, less has been reported about the possible impact of nutrition in the management of children with SMA type I.[8]

Of note, previous studies have reported more generalised metabolic abnormalities in SMA such as altered fatty acid metabolism, hyperlipidaemia, hyperglycaemia, hyperglucagonemia, increased hepatic insulin sensitivity and glucose intolerance.[9-11] Interestingly, lipid metabolism and fatty acid oxidation defects have been reported in early studies of patients with SMA where increased esterified carnitine and reduced β-oxidation capacity were observed.[12] Such perturbations could directly lead to impaired hepatic function, which is supported by the report of more than one-third of autopsies of children with SMA reveal liver steatosis on post-mortem necropsy.[13]

Current standard of care recommendations highlight the importance of a multidisciplinary approach in the management of SMA Type I which, includes nutrition and feeding as key components.[14, 15] Progressive muscle atrophy in children with SMA is accompanied with decreased lean body mass, increased fat mass as well as gastrointestinal symptoms such as gastro-oesophageal reflux disease and constipation.[16] Typically, long term nutritional support in the form of a gastrostomy is recommended as soon as oral intake is compromised.[17]

Recent studies led by our team working on SMA animal models support an independent and adjuvant role for nutrition in the absence of proactive respiratory care interventions.[11] Their data, and clinical experience, suggest a critical role for nutrition on quality of life in children with SMA.[18] The potential benefit of the synergistic effect of a specialised SMA diet and a drug in the management of SMA have been highlighted, which is highly relevant in the present therapeutic landscape.[19, 20]

Current dietetic recommendations for children with SMA is based on individual tolerance.[18, 21] However, an increasing number of families of SMA children are incorporating amino acid based enteral formulas into their child's feeding regimens. Originating from North America, the diet was designed and initiated by a SMA parents in the hope of improving SMA symptoms in their child. The diet has grown in popularity over the last few years following positive feedback from parents and individuals living with SMA, mostly via social media outlets.

Characteristics of the traditional amino acid formula diet (http://www.aadietinfo.com) include high carbohydrates, low fats, probiotics, vitamin D, co-enzyme Q10, branched-chain amino acid supplementation and oral hydration solutions. Anecdotally, families have reported improvements in their child's symptoms which are often associated with SMA including airway secretions, drooling, respiratory infections, constipation, and gastroesophageal reflux. Additionally, quality of sleep along with improvements in strength and stamina have also been reported to improve whilst following the SMA amino acid diet.[22] However, due to insufficient evidenced based research, clinicians are unable to prescribe or endorse the SMA amino acid diet, particularly in relation to associated risks between a high carbohydrate diet with hypertriglyceridemia[23, 24] and non-alcoholic fatty liver disease.[25, 26]

There is a need for a prospective clinical assessment to monitor the impact of an amino acid enteral formula on the common gastrointestinal symptoms seen in SMA Type I. Working with SMA families, we devised an adapted version of the traditional SMA amino acid diet. The proposed aim of this study was to assess the tolerability and safety of an adapted version of the traditional SMA amino acid diet

that contains an amino acid-based formula with added probiotics and additional carbohydrates (SMAAF).

METHODS

Patients

Children were recruited from our specialist tertiary neuromuscular SMA outpatient's clinic between June 2021 to May 2022. The inclusion criteria: a diagnosis of SMA Type I; which meant infants were aged over six months old; exclusively enterally fed via a feeding tube (meeting at least 90% of total energy intake from enteral formula); and experiencing at least one gastrointestinal symptom including (definitions outlined below). Exclusion criteria: children without SMA Type I; children meeting less than 90% of their total energy requirements from an enteral feeding tube.

The study was approved by the Health Research Authority, Integrated Research Application System (IRAS) 21/WS/0074 IRAS 295489. Written informed consent in accordance with universal good clinical practice guidelines in accordance with the ethical standards of the Helsinki declaration of 1975 was obtained from all parents of participants after discussing the objectives, study design, risks and benefits of participation before enrolment into our study.

Procedure

SMAAF was a single center prospective study. Recruited children were transferred on to an amino acid formula - (Neocate® Syneo™- Nutricia), which contains 34% medium chain triglycerides, 50% carbohydrate, probiotic-bifidobacterium, and prebiotic-fructo-oligosaccharide. SMAAD was followed for eight weeks; after two weeks on SMAAF additional carbohydrates (using Maxijul ® Super Soluble) were planned to be supplemented to 60% total energy intake. At the end of the eight-week trial children were to revert to their original enteral formula to compare gastrointestinal symptoms for another 4 weeks. Families were provided with components of SMAAF and a prescriptive individual

feed recipe during their outpatient visit. Table 1 highlights the difference in nutrient intake when comparing the traditional amino acid formula with SMAAF

Families had two in person meetings at baseline and week eight, with a telephone consultation at week four and six to monitor feed tolerance in respect to esophageal reflux, stool consistency and frequency (Figure 1). Parents were requested to report symptoms as either: improved, no change or worsened.

DATA GATHERING

Anthropometric Measurements

Weight (kg) and length (cm) measurements were collected at baseline (before changing to SMAAF) and on completion of the 8-week trial. All anthropometric measurements were collected during their routine neuromuscular outpatient clinic by trained clinicians using standardized conventional criteria and recognized measuring procedures.

Gastrointestinal Tolerance Monitoring

Stool consistency is a central component in the description of normal or altered bowel habit. Physical examination of stool can be considered as a proxy measure for stool consistency and refers to the shape and apparent texture of the stool, which can be assessed visually. Stool form scales are a standardised and inexpensive method of classifying stool into a finite number of categories that can be used by families and health care professionals. The Bristol Stool Scale is a visual stool form scale- the ideal stool is generally type 3 or 4, easy to pass without being too watery. Type 1 or 2 indicates constipation, whereas types 6 and 7 indicate loose stools.[27]

Tolerance and details of stooling patterns were recorded by families in weekly diaries. Descriptions of feed tolerance included the following variables:

Reflux - defined as parental observation of the passage of gastric contents into the oesophagus causing regurgitation, posseting or vomiting, which leads to troublesome symptoms that affect daily functioning [28]; constipation – defined as Rome IV Criteria, less than three defecations a week/ painful and hard stools [29]; persistent loose stools - lasting longer than 14 days, consisting of more than one loose stool a day. [30]

Oral Mucus Secretion Monitoring

Manual mechanical insufflation–exsufflation (cough assist) is the primary mode of airway clearance therapy performed by families. Families were asked to record in their weekly diaries the frequency and duration of their airway clearance individualised program including oral suctioning and mouth wiping for drooling.

Indirect Calorimetry Measurements

Indirect calorimetry was measured at baseline and planned to be repeated after eight-weeks on SMAAD (refer to protocol deviation below) to measure resting energy expenditure (REE) and respiratory quotient (RQ). An open-circuit ventilated-hood system calorimetric measurements were made using a portable metabolic cart (Q-NRG+ RMR, COSMED). It measures resting oxygen consumption (Vo2), carbon dioxide production (Vco2), and respiratory quotient. REE was auto calculated from these parameters using Weir equation. COSMED Indirect calorimetry was calibrated monthly, using a 2-point calibration method based on two separate mixtures of known gas content.[31]

Indirect calorimetry was completed by either GOC or SQ, with an early morning measurement (between 08:00 and 09:00) collected during the SMA outpatient day clinic, measured after an 8-h overnight fast to eliminate nutrient thermogenesis. The children lay awake, supine on a bed in a thermally neutral environment (24◦C) and were distracted by a portable screen to watch cartoons.

Statistical Analysis

Continuous quantitative data was calculated as mean and standard deviation. Z scores of weight-for-age and length-for-age, were computed based on UK-WHO growth data.[32, 33 34] The standard Student t-test was used to compare the weight mean Z scores before and after SMAAF. Analysis of variance was used to compare resting energy expenditure between predictive energy equations and indirect calorimetry. P value < 0.05 was required for statistical significance. Statistical analysis was performed with SPSS software (version 23, IBM SPSS Statistics, Armonk, NY, USA)

RESULTS

Fourteen children were recruited from June 2021 to May 2022, with a mean age of 4.1 years (±1.2 SD), of which 64% were female. The mean WAZ at baseline was -0.7 (±0.9SD). At recruitment, all 14 children required manual mechanical insufflation–exsufflation at least twice a day, with 11 of 14 (78%) requiring non-invasive ventilation - biphasic positive airway pressure for at least 12 hours. All children were receiving Nusinersen, an approved disease modifying treatment for SMA. Demographic characteristics of the cohort can be found in Table 2.

Most children (50%; 7 of 14) were on a standard 1kcal/ ml whole protein enteral formula prior to trialling SMAAF; whereas, 3 out of 14 (21%) were already on an amino acid formula (without probiotics). A full breakdown of feed formulas can be seen in Table 2. Indirect Calorimetry was measured at the start of the study to assess energy requirements and respiratory quotient. The mean resting energy expenditure was 803 kcal (±103 SD), which equated to 51.5 kcal/ kg (±7 SD). The mean respiratory quotient was 0.80 (±0.05 SD) (Table 3). An analysis of variance was used to compare resting energy requirements between indirect calorimetry measurements and predictive energy equations (Schofield equation [35] and Spinal muscular atrophy equation [31]) there was no significant difference

between values, p value 0.7 and 0.6, respectively (Table 3). A breakdown of key nutritional components of children on SMAAF can be viewed in Table 4.

The most common gastrointestinal complaint reported prior to switching to SMAAF was constipation, present in 12 of 14 (85%) children, of which 10 of the 12 (83%) children required daily stool softeners/laxatives were used to help regulate bowel function. Reflux was reported in 5 of 14 (35%) children (Table 4). Within one week of switching to SMAAF families reported a significant improvement in constipation symptoms.

Eight of the 10 (80%) children who received stool softeners/laxatives saw an improvement in constipation symptoms and either stopped or reduced medication (from daily to prescribed as required). All three children who were previously on standard amino acid formula prior to switch to amino acid formula with added pre and probiotics reported an improvement in stool consistency and frequency.

Stool consistency (as per Bristol stool chart classification) significantly improved from baseline compared to end of study (week 8) in children who switched to SMAAF; 2.2 (±0.4SD) vs 3.6 (±0.4SD) $p< 0.001$; CI 2.72-3.72, respectively. Similarly, stool frequency (bowel movements per week) increased from baseline compared to end of study (week 8) from 3.6 (±1.08SD) vs 4.9 (±0.45SD) per week; $p< 0.09$, CI -0.65-2, respectively.

Improvements in reflux was seen in 4 of 5 (80%) children, and a reduction in oral secretion was reported in 6 of 14 (43%) children (Table 5). Although some parents reported a reduction in reflux and oral secretion in respect to mouth wiping or mucus volume suctioned whilst receiving SMAAF, this was not captured in parent diaries and warrants further discussion how best to capture this outcome

Appropriate weight gain was observed while children were following SMAAF for the eight-week trial (baseline WAZ score: -0.7 [±0.9 SD] vs 8-weeks -0.5 [±0.7 SD], p=.03).

Adverse Events and amendments to original protocol

No participants experienced any serious adverse events. However, due to improved gastrointestinal symptoms within one week of starting SMAAF, only two families chose to add additional carbohydrates. Therefore, indirect calorimetry was not repeated at the end of the eight-week trial as there was no change in macronutrient intake. Furthermore, 12 of the 14 families refused to revert to their original feed formula after the eight-week trial. The two families who did revert to their previous formula reported resumption of constipation within one week and requested to restart SMAAF. An Amendment category C was submitted to the Health Research Authority to report changes to the original protocol: 295489 21SH01-2 17 Jan 2022 reference 143229.

DISCUSSION

With the development of disease modifying treatments children with SMA Type I are living beyond the previous four to five years life expectancy but continue to be affected by the highest disease burden. Our pilot study suggests that children with SMA Type I who are displaying gastrointestinal symptoms, especially when constipation is as a key feature of their clinical phenotype, may benefit from an amino acid formula.

It has been reported that 43% of children with SMA Type I suffer from severe constipation, with abdominal pain and meteorism reported in 15% and 14%, respectively[36]. This is significantly higher when compared to childhood constipation in the general population, which ranges from 0.7% to 29.6% (median 8.9; inter quartile range 5.3–17.4).[37] SMAAF, our simplified version of the traditional SMA amino acid diet had the most significant impact in children who suffered from constipation and required daily medication to regulate their bowel functions.

The cause of chronic constipation in children with SMA Type I is multifactorial, including reduced intake of fibre and fluids, gastrointestinal dysmotility related to a reduced tone and impaired strength of abdominal wall muscles.[38] Additionally, animal studies have also reported morphological (both gross and microscopic structural) changes within the gastrointestinal tract, along with alterations with

the enteric nervous system, resulting in inflammation and subsequent macrophage infiltration of the small intestine.[39]

Our study found an improvement in bowel function and cessation or reduction of constipation related medication in children who commenced SMAAD. Our findings are not only supported by the anecdotal reports from families but also by Bach et al. (2007) who performed a retrospective chart review and caregiver questionnaire on 103 families of children with SMA Type I. Of which, 57 children were on a modified amino acid diet, supplemented with B vitamins and minerals, glutamine, carnitine, long-chained free fatty acids, and probiotics - Lactobacillus. All the parents of the children using the modified amino acid diet reported one or more of the following benefits: decreased abdominal distention and constipation, improved oral secretions and reduced perspiration.[40]

Of consideration, an additional factor that may be contributing to constipation in SMA Type I is the chronic and ubiquitous use of prophylactic antibiotics in our cohort; prescribed to protect against opportunistic lung infections. Broad-spectrum antibiotics can affect the abundances of 30% of the bacteria in the gut community, causing rapid and significant drops in taxonomic richness, diversity, and evenness [41]. The routine practice of prophylactic antibiotic administration alters gut flora causing dysbiosis and may be contributing to the gastrointestinal complications seen in SMA Type I.[42, 43] Parents of children with SMA Type I have been adding probiotics to their child's amino acid diet to overcome the side effects of broad-spectrum antibiotics.[40]

A controversial component of the traditional SMA amino acid diet is its excessively high carbohydrate intake. The high carbohydrate and low-fat composition of the diet is hypothesised to be beneficial for children with SMA Type I by re-balancing the aberrant glucose levels, most likely caused by insufficient glycogen storage due to reduced muscle mass. Thus, a diet high in carbohydrate is thought to prevent hypoglycaemia.[44] Furthermore, the low-fat content can help with gastric motility and emptying which will reduce reflux.[45] However, excess glucose within the body is converted to triglycerides and stored as fat, contributing to total fat mass and hypertriglycaemia.[24] Of note, this practice of excessive

glucose intake may increase the risk of developing a fatty liver, a complication already seen in children with SMA.[13] Furthermore, the addition of carbohydrate module will add to the osmolality which may impact stool consistency and frequency [46]

Children with SMA have an inherent underlying liver abnormality, possibly due to abnormal fatty acid metabolism, and decreased stores of glutathione.[9] The exact mechanism of this fatty acid metabolism abnormality in SMA is unknown, but it is suspected to be related to loss of survival motor neuron function, correlates with severity of SMA, and is not directly related to a known genetic disorder of mitochondrial fatty acid oxidation.[20]

It appears that manipulating the type of fat in the diet may improve gastrointestinal symptoms and dyslipidaemia.[8] SMAAF contains 34% Medium Chain Triglycerides (MCTs), MCTs are more easily absorbed into the bloodstream from the gastrointestinal tract, unlike most other lipid molecules that require a complex process of digestion.[47] Dietary approaches aimed at modulating fatty acid metabolism defects and their subsequent effects on whole-body metabolic health are therefore an interesting strategy to improve quality of life of SMA patients.[8]

Further studies are needed to determine whether dietary manipulation used in mitochondrial long-chain fatty acid oxidation disorders[22] can also benefit children with SMA and ameliorate fatty liver pathology. However, manipulating the diet without specialist dietetic input may result in nutritional deficiencies as identified by Poruk et al., (2012) who monitored types of dietary intake and supplementation in children with SMA Type 1 between the first and last visits. The average length of time between the first and last visit was 18 months. The number of subjects following the traditional SMA amino acid diet increased from the first visit from 18 of 47 (38%) to the last visit to 23 of 34 (68%). The most common source of fat supplementation was safflower oil. Children in this study following an amino acids diet had a substantially lower percentage of fat intake and thus, lower intake of essential fatty acids. This may increase risk for essential fatty acid deficiency, further exacerbating the function of neurons and neurological system.[48]

Of note, despite children with SMA Type I having Body Mass Index (BMI) scores that correspond with normal or underweight, they also have an increased fat mass index (FMI), placing them in an overweight risk category.[19] Children with SMA Type I may have lower caloric requirements than healthy age-matched peers, increasing risk for over and undernourished states and deficiencies of critical nutrients. Standardized growth charts may overestimate faltering growth in SMA type I.[48] Due to this contradiction, BMI is considered an insufficient measure of adiposity in patients with SMA.[20] One proposed explanation for this inverse relationship between lower BMI and increased FMI is a discrepancy between energy intake and expenditure, a theory reflected in the disease's progression to immobilization.[49]

This physiological phenomenon is further reflected in our respiratory quotient findings collected from indirect calorimetry measurements. Respiratory quotient is a metabolic indicator based on the ratio of the volume of carbon dioxide produced and the oxygen consumed.[50] Our preliminary findings found a mean respiratory quotient similar to that reported by Bertoli et al (2017), with a RQ of 0.84 (0.05SD)[19], which is indicative of undernutrition and would suggest a need to increase total energy intake. This anomaly needs further investigation to ascertain if children with SMA are truly undernourished or whether this is just a reflection of an altered body composition.

Study limitations

This study is limited by its single centre nature, short duration, observational design without a control group, and small number of participants. Another limitation identified from this pilot study were parents' unwillingness to add carbohydrate or revert to their original enteral feed formula after SMAAF trial. Interestingly, these components of the trial were deemed important by families who were involved in the study planning phase. This deviation from the protocol would make a future randomised cross-over study untenable. Nonetheless, the safety and tolerance of an amino acid

formula with added probiotics in respect to constipation and other gastrointestinal management supports the need for further well controlled prospective studies.

CONCLUSION

Advances in SMA Type I therapy poses new challenges, particularly in relation to the management of gastrointestinal symptoms and liver disorders. Children with SMA Type I who are displaying gastrointestinal symptoms such as constipation and reflux may benefit from an amino acid formula that is fortified with probiotics. More research into fatty acid metabolism and manipulation of type of fats in children with SMA Type I is warranted.

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Figure 1 Timeline to highlight study procedure for children recruited to the Spinal Muscular Atrophy Amino Acid Formula Trial (SMAAF)

Table 1 Comparison of macronutrient composition for the traditional amino acid formula with SMAAF

Nutrient	Traditional AAF	SMAAF
Carbohydrates, %TEI	85	60
Fat, %TEI	5 (of which MCT 0%)	30 (of which MCT 35%
Protein, %TEI	10	10
Per 100ml		
Probiotics (CTU)	Variable	1 x 220
Prebiotics, g	Nil	1

Abbreviations: TEI; total energy intake. SMAAF; spinal muscular atrophy amino acid formula. AAF; amino acid formula. MCT; medium chain triglycerides

Table 2 The demographic characteristics of all children who changed on to Spinal Muscular Atrophy Amino Acid Formula (SMAAF)

Characteristic	
Sex, *N* (%)	
Male	5 (36)
Female	9 (64)
Age in decimal years, mean (±SD)	4.1 (±1.2)
Weight, mean (±SD), kg	14.8 (±1.9)
Weight Z score (±SD)	-0.7 (±0.9)
Height, mean (±SD), cm	98.0 (±8.6)
Height Z score (±SD)	-0.6 (±0.9)
Race/ Ethnicity, *N* (%)	
White/ White Other	8 (58)
Black African	1 (7)
Asian/ Asian Indian/ Asian other	5 (35)
Ventilation support, *N* (%)	
Self-ventilating in air	3 (21)
Non-Invasive Ventilation - overnight only	10 (71)
Non-Invasive Ventilation - dependent	1 (8)
Feeding route, *N* (%)	
Gastrostomy	12 (84)
Gastrostomy with jejunal extension	1 (8)
Naso Gastric Tube	1 (8)
Type of feed, *N* (%)	
Standard whole protein (1.0 kcal/ ml)	7 (50)

Low energy whole protein (0.7 kcal/ ml)	3 (21)
Hydrolysed Formula (1.0 kcal/ml)	1 (8)
Amino acid without Probiotics	3 (21)

Table 3 Comparison of baseline resting energy expenditure using different methods

	Indirect Calorimetry Mean (±SD) Kcal/day	Basal Metabolic Rate, Schofield Equation, mean (±SD), kcal/ day[35]	Spinal Muscular Atrophy, SMA Equation, mean (±SD), kcal/ day [31]	P value
Resting Energy Expenditure, mean (±SD) Kcal/ day	803 (±103)	789 (±90)	840 (±114)	0.7
Resting Energy Expenditure, mean (±SD), kcal/ kg	51.5 (±7)	52.6 (±7)	56 (±8)	0.1
Respiratory Quotient, *N* (%)	0.80 (0.05)			

Table 4 Nutrient intake of children on Spinal Muscular Atrophy Amino Acid Formula (SMAAF)

Nutrient Composition	**(n=14)**
Total feed volume, mean (±SD), ml/ day	866 (±186)
Concentration of Neocate Syneo, mean (SD), % *(Standard concentration of Neocate Syneo 15%)*	21.6 (±6)
Total energy intake, mean (±SD), Kcal/kg	58 (±14)
Protein, mean (±SD), grams/ kg	1.7 (±0.6)
Probiotics Bifidobacterium breve M-16V, Colony Forming Unit (±SD)	1 x 1897 (±562)
Prebiotics Fibre Oligofructose, mean (±SD), grams/ day	8.3 (±2.5)
Medium chain triglycerides, mean (±SD), grams/ day	13.9 (±4.2)

Table 5 Reported change in symptoms after children with SMA Type 1 changed to an Amino Acid Formula (SMAAF)

Gastrointestinal Intolerance Symptom	**Number of patients with symptom**	**Number of patients with improved symptoms post switch to SMAAF**	**P value (95% Confidence Interval)**
Reflux, *N* (%)	5/14 (35)	4/5 (80)	
Loose stools, *N* (%)	1/14 (7)	1/1 (100)	
Constipation, *N* (%)	12/14 (85)	10/12 (83)	
Of which on,			
Stool softener medication, N (%)	10/12 (83)	8/10 (80)	
Stool consistency, Bristol Stool Chart Category, (±SD)	2.2 (±0.4)	3.6 (±0.4)	0.001 (2.72-3.72)
Stool frequency - bowel movements per week, (±SD)	3.6 (±1.08)	4.9 (±0.45)	0.09 (-0.65-2.0)