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Comparison of horse and cow milk on sleep disorders in children with attention deficit hyperactivity disorder: a double-blind randomized clinical trial study

Seyedeh zahra Jokar[1], Tahereh Sadeghieh[2], Ruhollah Sadeghmanesh[3], Mehrdad Shakiba[4*]

[1]Department of Persian Medicine, The School of Persian Medicine, Shahid Sadoughi University of Medical Sciences, Ardakan, Yazd, Iran. [2]Child and Adolescent Psychiatrist, Researcher of Center of Addiction and Behavioral Sciences, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [3]Department of Otolaryngology-Head and Neck Surgery, Otorhinolaryngology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [4]Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

*Corresponding to: Mehrdad Shakiba. Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd 8951737915, Iran. E-mail: shakiba@ssu.ac.ir.

Abstract

Approximately 25%–50% of children with attention deficit hyperactivity disorder have sleep problems. The aim of this study is to compare the effect of horse milk with conventionally-fed cow's milk on sleep disorders in children with attention deficit hyperactivity disorder. In this randomized double-blind crossover study, 30 patients with attention deficit hyperactivity disorder were randomly selected and divided into two groups. All patients underwent a 45-day period of horse milk consumption and a 45-day period of cow milk consumption and they continued their drug treatment. A one-week interval between two periods of milk consumption was considered as the washout period. The severity of sleep disorder in the studied patients was determined based on the short form of the Children's Sleep Habits Questionnaire (CSHQ). Twenty-two (73.3%) male and eight (26.7%) female patients were included in this study. The mean age of the patients was 8.9 years. Our results showed that horse milk consumption improved the CSHQ score. For the group of patients consuming horse milk prior to cow milk, reductions of total CSHQ (P-value = 0.001) and subscale 1 (P-value < 0.001) scores were significant. For the group of patients consuming cow milk first, in addition to the total CSHQ (P-value < 0.001), subscale 3 (P-value = 0.001) and 4 (P-value = 0.009) dropped significantly. On the other hand, the results indicated that cow milk consumption increased the CSHQ score. Specifically, for the group of patients consuming horse milk first, the total CSHQ (P-value = 0.001), subscale 3 (P-value = 0.016), and subscale 4 (P-value = 0.010) increased significantly. The mean values of the first, second, third, and fourth subscales of CSHQ before and after the washout period were not significantly different between the two groups. According to the study, consuming horse milk was significantly better than cow milk in improving the total score of CSHQ in children with attention deficit hyperactivity disorder.

Keywords: Cow milk; Horse milk; Attention deficit hyperactivity disorder; Sleep disorder

Competing interests:

The authors declare no conflicts of interest.

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Abbreviations:

ADHD, attention deficit hyperactivity disorde; CSHQ, Children's Sleep Habits Questionnaire.

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Background

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodegenerative disorders in childhood [1]. It is characterized by problems in paying attention, excessive activity, or difficulty in controlling behavior [2]. The prevalence of this disorder is affected by age, sex, and ethnicity [3, 4]. ADHD is more common in males and affects 5%–10% of children at school ages [5]. The incidence of this disorder is 9.7% in Iran [6]. This disorder usually begins at the age of 2–4 years and often continues until adulthood [1, 7, 8]. ADHD is a multifactorial disorder which is affected by genetic and environmental factors [9]. Although the precise biological neurological mechanism of the disease is still not known well [10], some studies have shown that the receptor and transporter of serotonin, dopamine, and norepinephrine-associated genes are involved in the disease [9, 11–13]. The environmental factors affecting ADHD include thyroid disease, hypoxia, fever, as well as contact with chemicals, heavy metals, and organic pollutants. Additionally, nutritional factors of the neonate after birth are also associated with ADHD [14–17]. Furthermore, the diet has been considered as a culprit in ADHD [6, 18–20]. One of the important complications of this disease is sleep problems. There are four sleep disturbances associated with ADHD: difficulty falling asleep with ADHD, difficulty waking up with ADHD, intrusive sleep with ADHD, and restless sleep with ADHD. Treatment of ADHD can also improve sleep quality in children.

Currently, ADHD treatment types include behavioral therapy, psychotherapy, and treatment with drugs. Treatment with drugs usually involves long-term use of stimulants such as methylphenidate, dexamphetamine, and their derivatives, which results in enhanced activity of dopamine and norepinephrine [21, 22]. Nevertheless, approximately 30% of patients who receive stimulants do not show clinical progress or do not tolerate the drug [23]. On the other hand, there are some side effects after the use of drugs such as loss of appetite and weight, growth disorders, abdominal pain, headache, sleep problems, and even increased blood pressure [24, 25]. Long-term results in the study on children with ADHD in adulthood, both in the treated and untreated group, are disappointing [26, 27]. Some families are reluctant to use stimulant drugs or discontinue it arbitrarily or prefer to try complementary and alternative medicine [28, 29], herbal therapies [30, 31], and dietary supplements [32–34]. Studies have shown that the use of an appropriate diet may be effective in reducing the symptoms of ADHD and can be used as a supporting role along with drug therapy [35, 36]. Horse milk has long been used by humans. As some advantages of the milk selected as the candidate for this trial, it is rich in polyunsaturated fatty acids [36], is a good alternative for children allergic to cow's milk [37, 38], improves the immune system, and has anti-inflammatory properties with beneficial effects for the intestinal microbiome [39]. This study is designed to compare the efficacy of horse and conventionally-fed cow milk on sleep disorders in children with ADHD.

Methods

This study was conducted as a double-blind randomized clinical trial on patients with ADHD. The RCT has been registered with the Iranian Registry of Clinical Trials (IRCT) and provided with a registration number IRCT20170823035862N1 (https://www.irct.ir/search/result?query=IRCT20170823035862N1). Patients under study were selected from the age group of 6–14 years old (both sexes) referring to Shahid Sadoughi Hospital (Ethics Committee Approval Code: IR.SSU.REC.1396.52). Their parents signed the informed consent, while the patients above 10 years old patients also signed the informed consent.

The initial diagnosis of ADHD was based on the Connors criterion and face-to-face interview by a pediatric psychiatrist with the patient and his or her parents. Exclusion criteria were autism spectrum, mental retardation, schizophrenia, psychosis, mood or personality disorders, predominantly inattentive ADHD, premature or dysmature birth. The patients were randomized using a random number table and were divided into two groups (Figure 1). Both kinds of milk had the same smell, color, and taste. Milk bottles were coded and patients, patient's family, and the investigator were blind to the content of each bottle before collecting questionnaires. Two patients were removed from the study in the first week of the study because of irregular milk consumption. All patients underwent a 45-day period of horse milk consumption (250 cc daily) and a 45-day period of cow milk consumption (250 cc daily), and they continued their drug treatment. We provide pasteurized milk (63 °C/30 minutes) from a local milk supplier (the only horse milk supplier with a license from the Veterinary Administration in Yazd province). The milk was provided free of charge.

A one-week interval between two periods of milk consumption was considered as the washout period. The severity of sleep disorder in the studied patients was determined based on the short form of the Children's Sleep Habits Questionnaire (CSHQ). This form of CSHQ was recorded for each patient at the beginning of the study, at the beginning of each milk consumption period, and at the end of the milk consumption period. It includes 4 subscales (bedtime, sleep behavior, waking during the night, and morning wake up) and a total CSHQ. A higher score in each section indicates a more severe disorder. After collecting the data, the results were analyzed by

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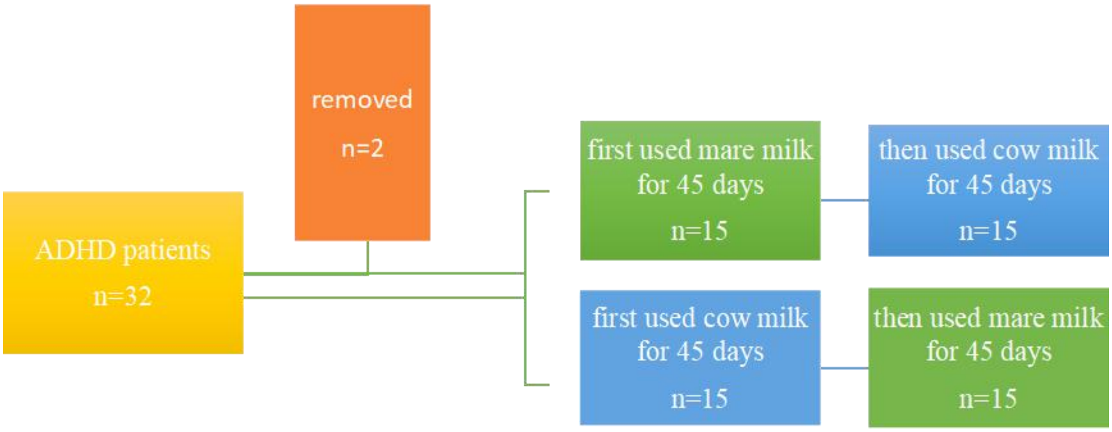

Figure 1 Flow chart for grouping patients

STAT-I-14 software and by the cross over data analysis. Finally, the effects of these two treatments were determined. The carry-over effect was also determined using the cross-over data model.

Results

A total of 30 patients with ADHD were studied who were randomly selected and divided into two groups. This study was a randomized, double-blind, and cross-over clinical trial conducted on female and male patients aged 6-14 years. In the present study, 22 (73.3%) patients were male and 8 (26.7%) were female, and the mean age of the patients was 8.9 years.

The first subscale of the CSHQ criterion

In the *t*-test performed in the group receiving horse milk first, the mean of the first subscale of CSHQ at the beginning of the study was 10.07 ± 2.37, which decreased to 6.53 ± 2.20 after horse milk consumption. Following the washout period, the mean of the first subscale of the CSHQ criterion reached 7.33 ± 3.10 and after the second period of milk consumption (cow milk consumption), it increased to 8.07 ± 3.24 (Table 1). In the *t*-test performed in the group receiving the cow milk first, the mean of the first subscale of CSHQ at the beginning of the study was 9.60 ± 3.71 which changed to 9.73 ± 4.07 after consuming the cow milk. Following the washout period, the mean of the first subscale of the CSHQ criterion reached 9.93 ± 3.65, and after the second period of milk consumption (horse milk consumption), it reached 9.20 ± 2.80 (Table 1).

In examining the effect of horse milk in the group which initially received horse milk, the mean of the first subscale of CSHQ diminished significantly after horse milk consumption (*P*-value < 0.001), but after the second milk consumption period (cow milk), CSHQ criterion did not rise significantly (*P*-value = 0.195). On the other hand, comparing the means of the first subscale of CSHQ at the end of two periods of milk consumption did not show any significant difference (*P*-value = 0.068) (Table 1).

In the group that first consumed cow milk, the mean of the first subscale of CSHQ did not change significantly after the cow milk consumption period (*P*-value = 0.751), and after the horse milk consumption period, the reduction in the mean of the first subscale of CSHQ was not significant (*P*-value = 0.052). Further, the means of the first subscale of CSHQ following cow milk consumption and after horse milk consumption were not significantly different (*P*-value = 0.229) (Table 1).

The means of the first subscale of CSHQ before and after the washout period were not significantly different in both groups (*P*-value = 0.152 in the group that first consumed horse milk and *P*-value = 0.334 in the group that first consumed cow milk) (Table 1).

The second subscale of the CSHQ criterion

In the *t*-test conducted in the group receiving horse milk first, the mean of the second subscale of CSHQ at the baseline of the study was 3.67 ± 3.01, which dropped to 2.93 ± 1.43 after horse milk consumption. After the washout period, the mean of the second subscale of the CSHQ criterion reached 3.40 ± 2.26 and after the second period of milk consumption (cow milk consumption), it rose to 3.87 ± 2.66 (Table 1).

In the *t*-test performed in the group receiving the cow milk first, the mean of the second subscale of CSHQ at the beginning of the study was 3.67 ± 1.58 which changed to 3.93 ± 2.12 after consuming the cow milk. Following the washout period, the mean of the

Table 1 Comparison of the mean of CSHQ criterion before and after milk consumption period

Variables		Mean				P value			
		I	AFM	BSM	ASM	Pv.1	Pv.2	Pv.3	Pv.4
Subscale 1	Group 1	10.07 ± 2.37	48.67 ± 8.38	7.33 ± 3.10	8.07 ± 3.24	0.000	0.152	0.195	0.068
(bed time)	Group 2	9.60 ± 3.71	9.73 ± 4.07	9.93 ± 3.65	9.20 ± 2.80	0.751	0.334	0.052	0.229
Subscale 2	Group 1	3.67 ± 3.01	2.93 ± 1.43	3.40 ± 2.26	3.87 ± 2.66	0.322	0.110	0.235	0.079
(behaviour)	Group 2	3.67 ± 1.58	3.93 ± 2.12	4.27 ± 2.21	3.33 ± 1.49	0.546	0.265	0.110	0.315
Subscale 3	Group 1	15.13 ± 7.04	11.33 ± 4.57	11.33 ± 4.43	12.07 ± 4.13	0.099	1.000	0.016	0.303
(sleep problems)	Group 2	13.80 ± 3.36	13.73 ± 2.60	13.20 ± 2.93	11.60 ± 2.69	0.898	0.120	0.001	0.000
Subscale 4	Group 1	24.33 ± 9.42	22.07 ± 7.27	22.00 ± 8.48	24.60 ± 8.32	0.236	0.950	0.010	0.027
(wake up)	Group 2	24.33 ± 9.42	23.53 ± 8.51	23.13 ± 7.24	20.13 ± 5.70	0.205	0.592	0.009	0.015
Total	Group 1	53.27 ± 11.08	42.87 ± 10.80	43.93 ± 11.87	48.67 ± 12.03	0.001	0.522	0.001	0.010
CSHQ	Group 2	48.67 ± 8.38	42.87 ± 10.80	50.53 ± 7.85	44.07 ± 6.17	0.115	0.699	0.000	0.001

Note: Group 1, first use horse milk then consume cow milk; Group 2, first use cow milk then consume horse milk; MCS, mean of CSHQ; I, initial of study; AFM, after first milk; BSM, before the second consumption of milk; ASM, after second milk; Pv.1, before and after the first milk consumption; Pv.2, before and after washout period; Pv.3, before and after the second consumption of milk; Pv.4, after the first and second consumption of milk; CSHQ, Children's Sleep Habits Questionnaire.

second subscale of the CSHQ criterion reached 4.27 ± 2.21, and after the second period of milk consumption (horse milk consumption), it reached 3.33 ± 1.49 (Table 1).

In exploring the effect of horse milk in the group first receiving horse milk, the mean of the first subscale of CSHQ declined significantly after horse milk consumption (*P*-value = 0.322), but after the second milk consumption period (cow milk), the increase in the mean second subscale of CSHQ was not significant (*P*-value = 0.235). Meanwhile, comparing the means of the second subscale of CSHQ at the end of two periods of milk consumption did not show a significant difference (*P*-value = 0.079) (Table 1).

In the group first consuming cow milk, the mean of the second subscale of CSHQ did not increase significantly after the cow milk consumption period (*P*-value = 0.546), and after the horse milk consumption period, the reduction in the mean of the second subscale of CSHQ was not significant (*P*-value = 0.110). Also, the means of the second subscale of CSHQ after cow milk consumption and after horse milk consumption were not significantly different (*P*-value = 0.315) (Table 1).

The means of the second subscale of CSHQ before and after the washout period were not significantly different in the two groups (*P*-value = 0.110 in the group first consuming horse milk and *P*-value = 0. 265 in the group first consuming cow milk) (Table 1).

The third subscale of the CSHQ criterion

In the *t*-test performed in the group receiving horse milk first, the mean of the third subscale of CSHQ at the beginning of the study was 15.13 ± 7.04, which decreased to 11.33 ± 4.57 after horse milk consumption. After the washout period, the mean of the third subscale of the CSHQ criterion reached 11.33 ± 4.43 and after the second period of milk consumption (cow milk consumption), it increased to 12.07 ± 4.13 (Table 1).

In the *t*-test conducted in the group receiving the cow milk first, the mean of the third subscale of CSHQ at the baseline of the study was 13.80 ± 3.36 which changed to 13.73 ± 2.60 after consuming the cow milk. After the washout period, the mean of the third subscale of the CSHQ criterion reached 13.20 ± 2.93, and after the second period of milk consumption (horse milk consumption), it dropped to 11.60 ± 2.69 (Table 1).

In testing the effect of horse milk in the group first receiving horse milk, the mean of the third subscale of CSHQ did not change significantly after horse milk consumption (*P*-value = 0.099), but after the second milk consumption period (cow milk), the mean of the third subscale of CSHQ increased significantly (*P*-value = 0.016). However, comparing the means of the third subscale of CSHQ at the end of two periods of milk consumption did not show a significant difference (*P*-value = 0.303) (Table 1).

In the group first drinking cow milk, the mean of the third subscale of CSHQ did not increase significantly following the cow milk consumption period (*P*-value = 0.898), but after the horse milk consumption period, the reduction in the mean of the third subscale of CSHQ was significant (*P*-value = 0.001). Also, the means of the third subscale of CSHQ after cow milk consumption and after horse milk consumption were significantly different (*P*-value < 0.001) (Table 1).

The means of the third subscale of CSHQ before

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and after the washout period were not significantly different in the two groups (*P*-value = 1.000 in the group first consuming horse milk and *P*-value = 0.120 in the group first consuming cow milk) (Table 1).

The fourth subscale of the CSHQ criterion

In the *t*-test performed in the group receiving horse milk first, the mean of the fourth subscale of CSHQ at the beginning of the study was 24.33 ± 9.42, which fell to 22.07 ± 7.27 after horse milk consumption. After the washout period, the mean of the fourth subscale of the CSHQ criterion reached 22.00 ± 8.48 and after the second period of milk consumption (cow milk consumption), it increased to 24.60 ± 8.32 (Table 1).

In the *t*-test performed in the group receiving the cow milk first, the mean of the fourth subscale of CSHQ at the beginning of the study was 21.60 ± 6.22 which changed to 23.53 ± 8.51 after consuming the cow milk. After the washout period, the mean of the fourth subscale of the CSHQ criterion reached 23.13 ± 7.24, and after the second period of milk consumption (horse milk consumption), it declined to 20.13 ± 5.70 (Table 1).

In examining the effect of horse milk in the group first receiving horse milk, the mean of the fourth subscale of CSHQ did not change significantly after horse milk consumption (*P*-value = 0.236), but after the second milk consumption period (cow milk), the mean of the second subscale of CSHQ increased significantly (*P*-value = 0.010). Comparison of the means of the fourth subscale of CSHQ at the end of the two periods of milk consumption showed a significant difference (*P*-value = 0.027) (Table 1).

In the group first drinking cow milk, the mean of the fourth subscale of CSHQ did not increase significantly after the cow milk consumption period (*P*-value = 0.205), but after the horse milk consumption period, the reduction in a mean of the fourth subscale of CSHQ was significant (*P*-value = 0.009). Also, the means of the fourth subscale of CSHQ after cow milk consumption and after horse milk consumption were significantly different (*P*-value = 0.015) (Table 1).

The means of the fourth subscale of CSHQ prior to and following the washout period was not significantly different in the two groups (*P*-value = 0.950 in the group first consuming horse milk and *P*-value = 0.592 in the group first consuming cow milk) (Table 1).

Total CSHQ

In the *t*-test performed in the group receiving horse milk first, the mean of total CSHQ at the beginning of the study was 53.27 ± 11.08, which dropped to 42.87 ± 10.80 after horse milk consumption. After the washout period, the mean of total CSHQ reached 43.93 ± 11.87 and following the second period of milk consumption (cow milk consumption), it increased to 48.67 ± 12.03 (Table 1).

In the *t*-test performed in the group receiving the cow milk first, the mean of total CSHQ at the beginning of the study was 48.67 ± 8.38 which changed to 50.93 ± 9.26 after consuming the cow milk. After the washout period, the mean of total CSHQ reached 50.53 ± 7.85, and after the second period of milk consumption (horse milk consumption), it declined to 44.07 ± 6.17 (Table 1).

In exploring the effect of horse milk in the group first receiving horse milk, the mean of total CSHQ decreased significantly after the horse milk consumption (*P*-value = 0.001), but after the second milk consumption period (cow milk), the total CSHQ increased significantly (*P*-value = 0.001). Comparing the means of total CSHQ at the end of two periods of milk consumption showed a significant difference (*P*-value = 0.010) (Table 1).

In the group first consuming cow milk, the mean of total CSHQ did not change significantly after the cow milk consumption period (*P*-value = 0.115), but after the horse milk consumption period, the mean of total CSHQ dropped significantly (*P*-value < 0.001). Also, the means of total CSHQ after cow milk consumption and after horse milk consumption were significantly different (*P*-value = 0.001) (Table 1).

The means of total CSHQ before and after the washout period were not significantly different in the two groups (*P*-value = 0.522 in the group first consuming horse milk and *P*-value = 0.699 in the group first drinking cow milk) (Table 1).

In the ANOVA test for the CSHQ criterion, the treatment effect was obtained at 0.106, the period effect 0.586, and carry-over effect 0.337, suggesting that the treatment effect was not significant. The order of consuming two types of milk (horse or cow) did not have a significant effect on the results of the analysis, and the effect of the first milk consumption in determining the CSHQ criterion obtained after the second milk consumption period was not significant either.

Discussion

Investigations have indicated that ADHD and sleep problems are related to each other with 25% to 50% of ADHD patients reporting sleep problems (because of ADHD or side effects of drug) [39]. In these children, a delay in sleep following a delay in melatonin secretion has been reported [40, 41]. The present study was conducted with the aim of comparing the effects of non-grass-fed cow and horse milk on the sleep of children with ADHD. In the present study, the mean of CSQH scores diminished significantly with horse milk consumption, but the order of milk consumption did not cause any significant difference. With regard to bedtime problems, horse milk consumption could significantly reduce these problems. Examination of sleep behavior indicated that the mean score of sleep was reduced, but the reduction was not significant. In investigating the problems of walking during the night, cow milk worsened sleep quality, but they were reduced with horse milk consumption, and the difference between horse milk and cow milk was significant. With regard to morning wake up, horse milk significantly improved the waking quality compared to cow milk, and waking problems were worsened with consuming cow milk. Horse milk can improve sleep due to its amino acids such as tryptophan, glycine, and L-glutamine, which are known amino acids associated with sleep. Also, horse milk contains vitamins (vitamin D, E, B6, B9), calcium, zinc, magnesium, iron, which are involved in sleep [42, 43].

Various studies have examined the relationship between some nutrient deficiencies and the severity of ADHD symptoms. For example, it has been indicated that lack of unsaturated fatty acids is associated with ADHD [44–46]. Horse milk contains high levels of unsaturated fatty acids. Compared to cow milk, horse milk has higher levels of a-linoleic acid and linoleic acid, which are precursors of omega-3 and 6 production [47–49]. Omega 3 and 6 are unsaturated fatty acids required for membrane fluidity, which are used as substrates for inflammatory eicosanoids and moderates dopaminergic neurotransmission, while also improving cellular performance [50, 51]. Numerous studies on mental diseases have shown that neuronal damage caused by oxidant substances plays a major role in these diseases. Several studies have investigated the association between ADHD and oxidative stress. Horse milk, compared to cow milk, has high levels of vitamin C, which can have good effects on ADHD symptoms due to its antioxidant effects [52–54].

Horse milk can play a probiotic role and increase Bifidobacteria in the human gut [55]. It has been observed that the consumption of these beneficial bacteria, known as probiotics, improves brain activity [56]. Studies have revealed that microbiota interacts with the neuroendocrine system (gut microbiome–mind–body chain) [57]. Studies have increasingly revealed the effect of gut bacteria on mood regulation, with the mechanism introduced as the gut-brain axis [58, 59]. Given that melatonin and serotonin hormones are required for good sleep, high levels of tryptophan in horse milk as a precursor of melatonin and serotonin can improve the secretion of these two hormones [60]. Some studies conducted on ADHD have shown that intolerance to some proteins can also be associated with this disease [61, 62]. Also, it is hypothesized that ADHD may be a type of allergic disease [63]. Thus, it can be a good alternative to cow milk in children who are allergic to cow milk [64, 65]. In Iranian traditional medicine, ADHD symptoms are associated with warm and dry temperament of the brain. Whey protein is one of the good compounds for the treatment of dry temperament whose level is higher in horse milk than cow milk [66, 67]. It should be noted, however, that holistic medicine has the highest efficiency when it provides therapeutic recommendations based on individual characteristics.

The time for prescribing horse milk and following-up patients was limited in our study and given that ADHD is a chronic disease, long-term follow-up is required to investigate the effects and possible side effects of horse milk. Furthermore, after the cessation of horse milk, the changes in CSHQ score were not re-examined to determine how long the desired effects of horse milk may last after cessation of milk. After ending the study, five families asked us to provide horse milk continuously. Since horse milk is expensive in some countries, it may not be economical to use it in the community for some families but in some countries horse milk is available and can be used as an alternative.

Other reasons could also explain our observation so it should be investigated by other researchers to evaluate our findings and its reproducibility. This study may give an idea that in children with ADHD, trying other kinds of milk may improve some aspects of their life. Although consumption of mare milk is not common as cow milk, this finding provides an opportunity to change the milk and improve the patient's quality of life in some cases.

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