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Editorial

Ketogenic diet: Old treatment, new beginning

Fasting has been an effective treatment of epilepsy since the Hippocratic era. Until the 19th century, epilepsy was believed to be a disease of 'eating too much'. Early in the 20th century, Guelpa and Marie, both French physicians, authored the first scientific report on the value of fasting in epilepsy (Guelpa and Marie, 1911). As simple fasting could not be maintained by epileptic patients for a sufficiently long period, in 1921, Dr. Wilder in Mayo clinic suggested that a high fat diet and resulting ketonemia may improve seizures and he named this high fat diet the ketogenic diet (KD). KD means ketone producing diet. He reported three refractory epileptic patients whose seizures were dramatically reduced after KD (Wilder, 1921). Although KD was started in the field of epilepsy early in the 20th century, it was not used frequently until the late 20th century because new anticonvulsants were developed, methods of KD was complicated, and patient adherence was poor. After many reports of a pronounced effect of KD on refractory childhood epileptic syndromes were published, it became more popular.

Currently, KD includes classic ketogenic diet, the medium chain triglyceride (MCT) diet, the modified Atkins diet (MAD) and the low glycemic index treatment (LGIT). These different KDs are differ in the ratio of fat to carbohydrate and protein grams combined. A 4:1 ratio is more strict than a 3:1 ratio and is generally more effective but harder for patients to adhere to it. So a more strict regimen is used for the infants and children. As successful treatment of KD largely depends on the adherence of patient, cooperation among physician, dietician, family, and patient is utmost importance.

The KD has been used as a therapeutic alternative to antiepileptic drugs (AEDs) for the treatment of refractory epilepsy and usually reserved for young patients who have seizures that are difficult to control. Recently, KD is alternative treatment option in the treatment of super-refractory status epilepticus (SE) in many centers and the age of patients who are treated with KD is getting older (Cervenka et al., 2017). Also, KD can be used in the treatment of obese diabetes mellitus type II patients (Boden et al., 2005), or as an adjuvant treatment of some cancer therapies (Erickson et al., 2017). In the neurological field, many of neurodegenerative diseases or neuromuscular disorders such as mitochondrial diseases may be helped by KD as well (Paoli et al., 2014).

The anticonvulsant action of KD in epilepsy still needs to be elucidated. Although the exact mechanisms of KD in lessening seizure activity remain unknown, serum ketone bodies change neuronal metabolic status, and have an influence on the neuronal transmitter number and function as well as regulating neuronal development. So, there are multiple mechanisms that target biochemical pathways linked to cellular substrates (e.g., ion channels) and mediators responsible for neuronal hyperexcitability. KD causes interactions with receptors, channels, and metabolic enzymes. Decanoic acid, a component of medium-chain triglycerides, contributes to seizure control through direct α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor inhibition. It also affects DNA methylation (Boison, 2017) and it may enhance the binding potential of benzodiazepine receptors (Kumada et al., 2012).

The effects and adverse events of KD have been documented in a number of case reports and case series to be particularly helpful for some epilepsy conditions. KD is a first-line treatment option in certain genetic syndromes of glucose transporter type I deficiency or pyruvate dehydrogenase deficiency. Other epileptic syndromes with good efficacy of KD are infantile spasms, Rett syndrome, tuberous sclerosis complex, Dravet syndrome, Doose syndrome, etc. But as most studies were reported from a single center or in single case series, reliable information on efficacy and adverse events of KD are sparse. The reasons why we do not have a RCT of class 1 evidence study with KD are 1) we do not have a uniform protocol for KD; 2) KD is still not familiar to many epileptologists especially for treating adults; 3) maintaining KD is not easy for many patients; 4) concerns about the optimal management of unusual adverse events of KD.

Williams and Cervenka (2017) extensively reviewed on the efficacy of KD in the treatment of chronic, refractory epilepsy and super-refractory SE. After review of current status of KD in clinical practice, they proposed guidelines for the implementation and maintenance of KD in these disorders. They summarized minimum standards and recommendations of pre-diet evaluations and follow-up visits and those for the common adverse events of renal stone, hyperlipidemia, fatty liver, and osteoporosis. Nutritional, laboratory, and diagnostic issues were summarized. In these guidelines, they briefly commented on the common adverse events of KD and their appropriate management.

KD as a treatment option in super-refractory SE needs additional comment. Although the number of patients with super-refractory SE treated with KD were not more than hundreds in the literature, the reported success rate is quite high and adverse events were not critical for most patients. Most of the patients were very refractory SE such as NORSE, encephalitis including immune-mediated encephalitis or epileptic encephalopathy. The evaluation of specific treatment in super-refractory SE is not easy because the patients already take more than 4–5 drugs including sedatives, but additional KD usually induces improvement in less than a week even with no additional treatment. As pointed out by Williams and Cervenka (2017), ICU setting affords good

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conditions to start, monitor, and maintain the diet. Therefore, adverse events can be detected earlier and the needed duration of maintaining KD is relatively short. Most of the patients treated in an ICU setting discontinued ventilatory support within two weeks.

KD is an old method of treating refractory epilepsy, but with an enormous recently published favorable clinical data. It is just beginning a broader application in the field of refractory epilepsy and super-refractory SE.

Conflict of interest

None.

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