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Rare Side Effects of the Ketogenic Diet, a Tertiary Hospital Experience

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Abstract

Quite few centers in the Middle East are offering the ketogenic diet therapy for the treatment of epilepsy in patients with drug refractory seizures. In King Fahad Medical City, National Neuroscience Institute, Department of Pediatric Neurology, there started the ketogenic therapy program in November 2008. Since then, interesting cases that are seldom encountered by many physicians during their medical careers as well as lab work that is unforeseen and deemed interesting, were observed, and collected. Here we try to exhibit these interesting cases and display unexpected laboratory results. We raise questions more than answers, as searching medical literature and personal communication could not bring clear answers. We quickly review results of patients' responses and failures to the diet.

Keywords: Ketogenic diet; Seizures; Epilepsy; Refeeding syndrome; Electrolytes

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Introduction

Since early history of human being, natural body defense mechanisms were the first lines of protection. With the exception of few diseases, anorexia appears to be the first reflexive mechanism following illnesses. Fasting as a voluntary cessation of eating practiced in different ways, proved to be beneficial in health issues through multiple mechanisms [1]. This might be a source of autophagy or might be the basis of another enigmatic defensive mechanism.

Fasting was thought of, as a way of antiseizure treatment since olden times, consequently simulation and augmentation of fasting in a more prolific way was deemed a trend of treating seizures. Since the time of Wilder et al. [2] Ketogenic Diet (KD) has been known for the high content of fats and the lower than average protein supply and the very low amount of carbohydrates. The different forms of the diet proved to be effective in treating all types of epileptic seizures, with more valuable responses in certain epileptic syndromes as compared to others [3]. The number of written articles on the KD is expanding each moment. The use of the diet is widely expanding to include lots of health conditions that are related or unrelated to seizures. All over the world, the number of hospitals and health centers using the diet is increasing. In the Middle East there are around 20 centers using the diet (personal communication). One of those is our center in Riyadh, KSA which started in late 2008 [4].

Here we are not trying to prove the success of the diet in treating seizures including the very difficult to control ones, but we aim to bring aspects that are scarcely mentioned in the literature. This included rare side effects and their treatment, occasional associations that are worth to be acknowledged by junior physicians and dietitians who are interested and willing to work in the KD field.

We discuss as well certain genetic affections and relation to a good response to the diet as this is deemed interesting. Laboratory results that had no clear explanation were presented as well. We will not discuss in details the information that have been exhaustingly discussed in many previous articles e.g. response to the diet, numbers receiving each type of diet, and all other repetitively discussed and established issues.

Materials and Methods

Type of the study: Retrospective prospective cohort study.

Place of the study: King Fahad Medical City, Pediatric Neurology Ward and/or Epilepsy Monitoring Unit in the National Neuroscience Institute.

Patients: Patients who were admitted for initiation of the diet, regardless of their age or diagnosis

Inclusion criteria: All patients that were treated with KD in our hospital who agreed to be included in the study. This included most of patients who were taken care of in the KD program through the period from November 2008 till June 2020.

Exclusion criteria: Refusal to be included in the study was rated as an exclusion criterion.

Admission and Investigations: 160 patients agreed to be included in the study. Most of the patients were admitted for 3 days.

Course in the hospital: during admission: full examination was done, and body parameters were taken. Laboratory work was sent as per protocol.

On the first day of admission, children were started on 1:1 classic KD, followed by 2:1 the following day and then 3:1 on the third day. Meanwhile, mothers were taught the essence of the KD, benefits and hazards of the diet, possible side effects and how to prepare the diet. The social worker used to visit all families and their children before starting the diet. The clinical pharmacist of the KD team used to visit them on day of admission to adjust and modify drug treatment to more suitable forms that are sugar or nearly sugar free to be compatible with the diet. Parents were taught what to do if by mistake, the child received unnecessary sugar/glucose. They were told about clinical manifestations of hypoglycemia and how to deal with it, how to measure glucose and ketones.

After three days, most of the patients were discharged to be followed up after four weeks and accordingly. During the initial care and follow up, interesting cases and side effects were encountered, and peculiar laboratory findings were reported.

Our aim is to mainly discuss these rare findings and to briefly summarize our patient results. To avoid unnecessary elongation our results will be displayed merely as per paragraphs without further index comments (Figure 1, 2). The top two diagnoses were Infantile Spasms (IS): 24% and Lennox Gastaut Syndrome (LGS).

The majority (81%) of patients had generalized seizures, mainly of tonic-clonic type (32%), followed by infantile Spasm (23%), and then multiple seizure semiology (21%) (Figure 3).

In our cohort, 20% of patients with Autistic Spectrum Disorders (ASD) showed improvement in the autistic features.

As seen in Figure 4, 43% patients had diffuse brain atrophy on MRI, and 18% had Hypoxic Ischemic Encephalopathy (HIE) picture.

Patient's weight was measured on three points of time, at starting the diet, after 6 months of the diet, and in the end of the diet. The weight was categorized into 3 categories: <50 percentile, 50 percentile, and >50 percentile.

Patients in the 50 percentile or below almost remained the same, in the first six months period, but their weight decreased in the end of KD. Patients who were above 50 percentile showed increase in weight after the period of 6 months.

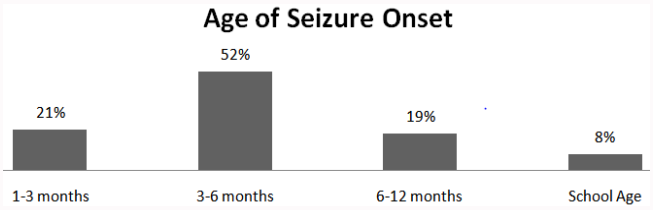

Figure 1: Shows age of seizure onset.

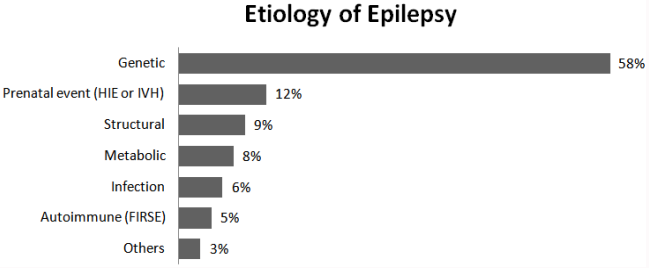

Figure 2: Shows different etiologies of patients' seizures.

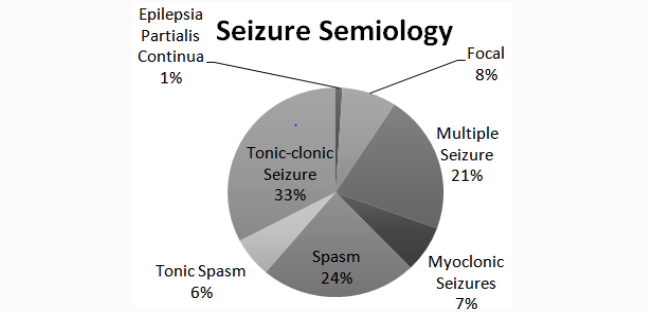

Figure 3: Types and semiology of encountered seizures.

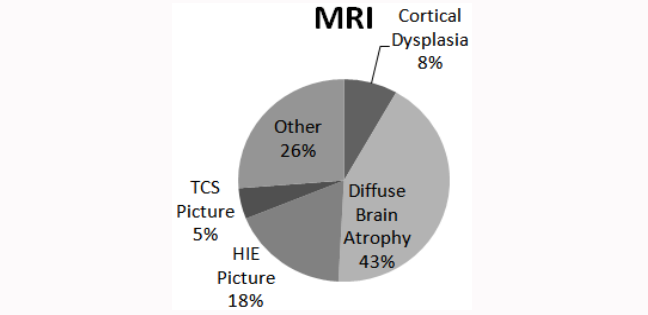

Figure 4: MRI brain findings.

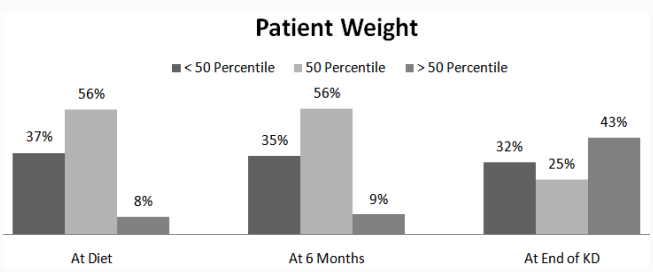

Figure 5: Patient weight at different points over time of diet.

Seven percent of the patients could not continue the diet, where families could not follow the instructions in 39%, while 28% had no

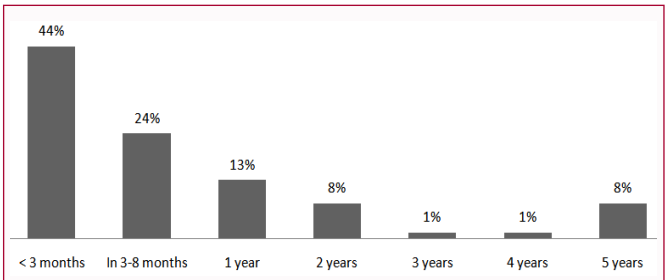

Figure 6: Shows time of discontinuation of the diet.

	Case %
Nausea or Vomiting	20.7
Constipation	22.3
Diarrhea	0.8
Electrolyte Imbalance	9.1
Infection	6.6
Hypoglycemia	11.6
Abdominal Pain	6.6
Hair Loss	4.1
Behavior Disorder	5.8
Renal Stones	1.7
Dehydration	1.7
Prurigo Pigmentosa	7.4
Refeeding Syndrome	0.8
Pancreatitis	0.8
Total	100

Figure 7: All the side effects resolved either spontaneously or with minimal manipulation.

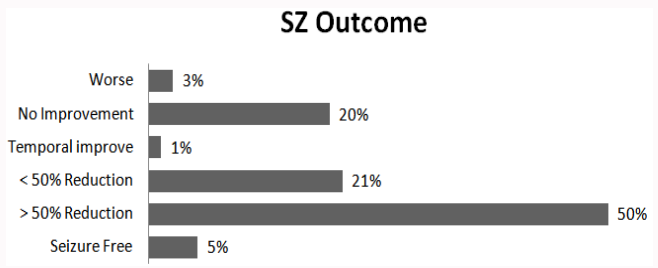

Figure 8: Seizure reduction.

improvement, and 24% experienced side effects (Figure 5). Some families were willing to continue the diet for unlimited time (Figure 6). The side effects of the diet are presented as percentages in Figure 7.

All the side effects resolved either spontaneously or with minimal manipulation.

The majority of patients showed more than 50% seizure reduction in frequency and or severity (Figure 8). Among our patients, there were cases that developed side effects of the diet that are worth mentioning and illustrating their treatment.

Glucose 6 Phosphate Dehydrogenase Deficiency

A nine year old boy with LGS and developmental regression. His seizures started at the age of six months. He had corpus colostomy recently. His seizures did not show improvement and he was admitted for KD trial.

Seizures used to be tonic, atonic, eye up rolling and staring episodes 3 to 4 times daily apart from the eye up rolling which were very frequent but each lasting few seconds.

He is on Valproic Acid (VPA), Rufinamide (Ruf) Topiramate (TPM), Clobazam (Clbz) and Levetiracetam (LEV). He failed Phenobarbital (PB) and Lamotrigine (Ltg). He had history of three times status epilepticus and Pediatric Intensive Care Unit (PICU) admission.

Sleep deprivation was apparently the precipitating factor. He was born at term and had neonatal jaundice upon delivery that required phototherapy for 3 days. He was discovered to have G6PDD. According to family, he did not have further attacks of hemolysis, as they were keen and avoided all kinds of precipitants.

He showed developmental regression at the age of six months, started follow up in a peripheral hospital at the age of one year, and then sought medical advice in different hospitals and lately at our institute.

He had global delay in particular cognitive delay. He had his vaccination up to age and is not known to have certain allergies. Parents are healthy cousins with two other healthy siblings. No family history of epilepsy or febrile seizures.

CGH-Micro-array revealed a male genomic profile with a gain of 384 kbp detected in x chromosome 28, involving the 16 genes, duplication of MECP2 gene, was associated with lubs x linked mental retardation syndrome. Brain MRI showed bilateral cystic foci most likely periventricular leukomalacia. No other significant abnormalities.

He was admitted to try KD (Not knowing that he has G6PDD) hoping to ameliorate his seizures. Unfortunately, while he was in hospital and on nearly 1.2: 1 KD ratio, he got hemoptysis. We discontinued the diet and hemoptysis stopped. He was transferred to our epileptologists for further management of seizures and follow up. The issue we are trying to raise here is the relation between KD and G6PDD. We could not find, after effortful search and personal communication, an explanation to the hemoptysis which followed the KD in low ratio and was reversible after its discontinuation.

G6PD deficiency, a defect in the hexose monophosphate shunt pathway, is the most common disorder of Red Blood Cell (RBC) metabolism [5]. It is an X linked disease affecting mainly boys. The disease has high amount of variation that are classified I through V by the amount of activity of the G6PD enzyme [6].

G6PD deficiency renders RBCs susceptible to oxidative stress, which shortens RBC survival. Hemolysis occurs following an oxidative challenge, commonly after fever, acute viral or bacterial infections, and diabetic ketoacidosis [7]. KD is proved to possess antioxidant and anti-inflammatory properties [8]. One of the mechanisms claimed is the capability of the KD to influence the microRNA (miR) expression profile. And as regulators of the metabolic network in which Radical Oxygen Species (ROS) are always produced, these miRs are also able to counteract inflammatory and oxidative stress [9].

Then there should be another explanation why the KD was stressful and hemoptysis inducing in this child, an explanation that we could not illustrate.

Refeeding Syndrome

Case 1A

The patient is a nine year-old girl, with epileptic encephalopathy,

Table 1: Weight of the patients over different periods.

Weight	At Diet Onset	At 6 months	At 12 Months
Percentile	15 kg	11.1 kg	8 kg

Table 2: Case 1A electrolytes.

Electrolytes	Percentage
Potassium (3.3-5.0 mmol/l)	2.8
Magnesium (0.6-1.1 mmol/l)	0.57
Urea (2.6-7.0 mmol/l)	9.5
Creatinine (44-88) umol/L	20
Phosphate (0.8-1.4 mmol/l)	0.68
Albumin (35.0-55.0 g/l)	22

secondary to loss of function mutations in UDP-Glucose 6-Dehydrogenase. She has spastic quadriplegia, global developmental delay, and swallowing in coordination, and is on GT feeding.

She was on KD for intractable epilepsy, at a ratio of 3:1, for 2 years. She was seizure free while on the KD. During the diet, the patient had significant weight loss, to 50% of her original weight (Table 1).

The patient was given a plan to resume their normal diet gradually. However, the family did not follow the team's instructions. They resumed regular diets faster than planned to swiftly gain weight. One month later after discontinuing the KD, the patient came to our Emergency Room (ER) with a decreased level of consciousness. The patient had no history of fever, respiratory tract infection, or increased seizure frequency.

Growth parameters were all below the third centile.

- In ER patient was afebrile, unresponsive, with shallow breathing, and GCS of 4/15. She was intubated and admitted to PICU.
- Blood pressure: 97/63 mmHg. Pulse: 50/min. Respiratory rate: 10/min. 02 saturation: 76% in room air. Despite good bilateral airway entry.
- Cardiovascular: Normal first and second heart sound, no added sounds.
- The abdomen was soft, lax with no organomegaly
- There was lower limb edema.

In PICU, she was started empirically on vancomycin, ceftriaxone, and acyclovir that were discontinued after negative cultures. Considering the electrolyte disturbances, low albumin (Table 2), and the clinical scenario, the patient was diagnosed with refeeding syndrome.

Patient (Figure 9) was kept Nil per OS (NPO) for 2 days and started on IV fluids. On day 3, she was started on 50% of her feeding requirement to be increased by 10% every other day until it reached 100% of her need. The patient began potassium, phosphate, Mg, replacement, and albumin infusion and was sent home in a stable condition on phosphate replacement.

Case 2A

The patient is a nine-year-old boy (Figure 10), with unremarkable health history. He was doing fine till he started to have fever 37.9°C with no other complaints. Then he started to have sudden onset of left sided seizures evolving to generalized tonic-clonic, very frequent and refractory to treatment. For that, patient was intubated at ER and

Figure 9: Case1A with severe cachexia.

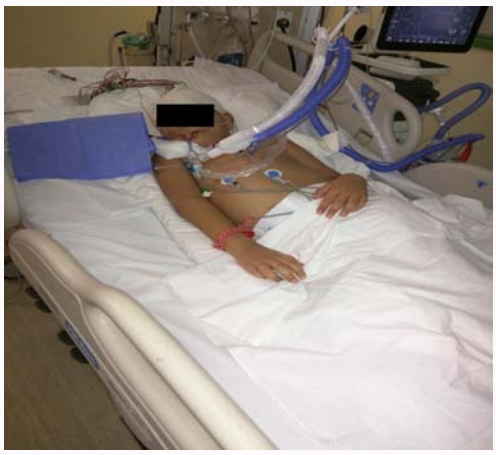

Figure 10: (Case 2A) the patient is a nine-year-old boy, with unremarkable health history.

Table 3: Case 2A electrolyte.

Biochemical parameters	Day 1
Sodium (135.0-147.0 mmol/l)	136
Potassium (3.3-5.0 mmol/l)	3.1
Magnesium (0.6-1.1 mmol/l)	0.55
Urea (2.6-7.0 mmol/l)	3.5
Creatinine (44-88) umol/L	44
Phosphate (0.8-1.4 mmol/l)	0.58
Albumin (35.0-55.0 g/l)	34

shifted to PICU.

He received infusion of Midazolam (MDZ), Propofol (PPF), and LEV in addition to TPM, Phenytoin (PHT) and PB with no improvement. Initial CT showed brain edema. He received 3 doses of IVIG as well as pulse steroids.

He was transferred to our hospital PICU, on the above medications and he was having active clinical seizures manifested as mouth twitching and upper limb tonic-clonic movements. He was diagnosed with possible Febrile Infection-Related Epilepsy Syndrome (FIRES).

He was started on thiopental, Ketamine, and MDZ in maximized

doses. We initiated Lacosamide (LAC) and KD starting as 1:1 then increased gradually to reach 4:1. PPF was weaned until it was discontinued to avoid any interaction with the KD. Unfortunately, he developed diarrhea and did not respond to the diet, so it was discontinued. Electrolyte imbalance with hypophosphatemia, hypokalemia, and hypomagnesemia followed and he was diagnosed with refeeding syndrome (Table 3). Supplementation of lost minerals as well as gradual introduction of normal diet helped return to his base line regarding the refeeding consequences. Anakinra for FIRES was started, but child did not respond.

Refeeding syndrome is a complex syndrome that includes abnormal sodium and fluid balance; changes in glucose, protein, and fat metabolism; thiamine deficiency; hypokalemia; and hypomagnesemia [10]. The hallmark biochemical feature of refeeding syndrome is hypophosphatemia.

Rapid refeeding whether enteral or parenteral causes metabolic and hormonal changes. As in early starvation, the body switches from using carbohydrate to using fat and protein as the main source of energy, the basal metabolic rate decreases by as much as 20% to 25% [11].

Certain hormonal and metabolic changes try preventing protein and muscle breakdown during prolonged fasting. Tissues, in particular muscles decrease their use of ketone bodies and start using fatty acids as the main energy source instead. This results in an increase in blood levels of ketones, switching the brain from glucose to ketone bodies as its main energy source. In order to preserve the muscle protein, the liver decreases its rate of gluconeogenesis [12].

Despite the poor supply of minerals during periods of prolonged starvation, serum concentrations of these minerals (including phosphate) may remain normal. This is ascribed to the fact that these minerals are mainly in the intracellular compartment, which contracts during starvation. In addition, there is a reduction in renal excretion.

The incidence of refeeding syndrome is unknown. This in part is due to the lack of a universally accepted definition. A study of around ten thousand hospitalized patients, the incidence of severe hypophosphatemia was 0.43%, with malnutrition being one of the strongest risk factors [13].

When a patient rapidly shifts from ketogenic diet with its restricted carbohydrates to normal foods with normal or high content of carbohydrates, the rise of blood glucose increases insulin with consequent decrease of secretion of glucagon. Insulin stimulates glycogen, fat, and protein synthesis, a process that requires minerals such as phosphate and magnesium, and cofactors such as thiamine [14].

The sodium-potassium ATPase symporter transports glucose and potassium to be absorbed into the cells, a process that is stimulated by insulin. Magnesium and phosphate are also taken up into the cells and water follows by osmosis [15].

The consequent depletion of phosphate, potassium, and magnesium serum levels and the rapid change in basal metabolic rate are the essence of the clinical features of the refeeding syndrome [16].

As per literature, patients at high risk of refeeding syndrome are those with anorexia nervosa, chronic alcoholism, oncology patients, postoperative patients, elderly, and those with uncontrolled diabetes and those with chronic malnutrition [17].

Refeeding syndrome has been reported with all such cases (Vide supra). Search revealed no previous reports on the association of the syndrome with the ketogenic diet.

In our center, the syndrome occurred in 2 patients: One boy who was admitted with FIRES and the other with loss of function mutations in UDP-Glucose 6-Dehydrogenase causing recessive developmental epileptic encephalopathy.

Prurigo Pigmentosa

Case 1B: A seven year old boy with Dravet syndrome, started to have seizures in infancy including generalized tonic, tonic clonic atypical absences and myoclonic. He was on clobazam, valproic acid, carnitine and stiripentol. He was fairly controlled on the ASMs. Family was aiming to boost the seizure responses by adding KD. The seizures showed better responses with 90% or above seizure control. One month after starting the KD and while on 4:1 ratio, he started to have ecchymotic lesions (Figure 11) that were painless with no itching and with normal platelet count and coagulation profile. We discussed with the family the option of not changing the diet ratio and to observe. The family agreed and the rash disappeared gradually and completely within three months.

Case 2B: At the age of 7 months, this girl with CDKL5 started to have infantile spasms and her seizures failed to respond to ACTH, Vigabatrin (VGB) and LEV. She was referred to us for KD trial at the age of one year. She was tried on 3:1 KD. She started to show fairly good response (80% seizure reduction), but unfortunately there was no compliance.

Soon the child got netlike rashes (Figure 12) that were ascribed to KD. The family was unwilling to continue the diet and they were told that the rash might respond to cessation of the diet therapy. Within few days the rash started to gradually fade away without specific treatment. Worth to mention that the child was seen by dermatologists who prescribed ointments for the rash, but unfortunately it did not show any response. She was referred to the epilepsy program. Another male with CDKL5 got a similar rash on 2:1 KD ratio.

This condition was initially reported in 1971 in Asian women [18], but with time it was described in different ethnicities and in both genders and even in twins [19]. An association between KD and PP was reported in 3 cases in Saudi Arabia [20]. Association with conditions like atopy, *H pylori* infection and Sjogren's syndrome was published [21].

While the etiology of Prurigo pigmentosa is yet unknown, it has been strongly associated with conditions that commonly produce

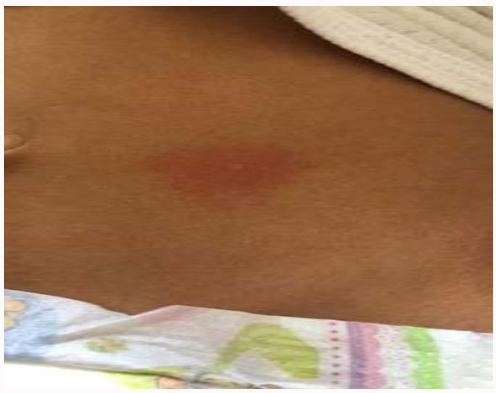

Figure 11: (Case 1B) A seven year old boy with Dravet syndrome.

Figure 12: (Case 2B) - At the age of 7 months, this girl with CDKL5 started to have infantile spasms and her seizures failed to respond to ACTH, vigabatrin and levetiracetam.

ketosis, such as restrictive dieting, fasting, and uncontrolled diabetes mellitus.

Whether it is caused by irritation of blood vessels by ketones, causing an inflammatory response manifesting as an itchy rash or diet-related gut microbiome changes that affect the immune system, is not known for sure. Other hypotheses are possibly skin irritation from acetone that is released in sweat, and an atypical response to low insulin levels that occur during ketogenic eating or fasting [22-24]. When PP is experienced by those who are on ketogenic diet, it is called Keto rash which has been recently reported [25].

It is itchy, red rash that typically occurs on the torso, back, neck, and underarms. The rash is often symmetrical and usually appears within a few days or weeks of entering ketosis. It has a net like pattern throughout its course. It can pass through stages of being a macule, a papule and a vesicle or a pustule [26]. It may resolve spontaneously but may also reportedly persist for several months or even years [27]. Diet modification as a sort of treatment of PP was reported [28]. Between our candidates on KD we got 6 patients who presented with the rash. In our cases we found that the treatment might prove different in different patients. One patient needed decrease of the KD ratio, another needed just changing the KD stuffs and the third needed to just wait and see. We presented a couple of cases as all ran same scenario. The photos of those two patients are shown (Figure 11, 12).

Hypervitaminosis D

A 13 years old boy with spastic quadriplegic Cerebral Palsy (CP) 2ry to HIE. He started to have seizures at 4 years of age that are not responsive to ASMs. He got multiple fractures and was detected to have very low vitamin D level.

He was referred for KD at the age of 11 years. He responded well with disappearance of 80% of seizures. He was given therapeutic doses of vitamin D and fractures were healing. On follow up, he got significant loss of weight, necessitating increase of calories. His weight did not improve; on the contrary, he was losing weight. In addition, he started to have fatigue, loss of appetite, excessive thirst, excessive urination, dehydration, constipation, irritability, nervousness and non-suppurative conjunctivitis.

Manipulation of the diet failed to improve his condition. Considering the clinical scenario, we thought of hypervitaminosis D.

Vitamin D level was found to be overly high. Vitamin D supplementation was stopped, and he showed gradual improvement; but mother was reluctant to continue the diet.

We learned to carefully observe vitamin D levels when it is combined with KD, as the latter might facilitate vitamin D absorption leading to unexpected high body levels even with doses in the therapeutic range.

Persistent and resistant hypokalemia

Two years old boy who got infantile spasms at age of four months that responded to VGB which was discontinued after three months of use. Recurrence occurred at age of nine months and repeating trials of VGB failed to control the seizures that were exacerbated by LEV, did not respond to clobazam and was refectory to TPM.

After starting the diet, the child was persistently hypokalemic. Replacement with potassium citrate up to10 MEQ TID (3 meq/kg/day) failed to correct the hypokalemia. Surprisingly, we noticed that the more K we continued to give, the lower the blood level of K it was getting.

He was referred to nephrology team who declared that kidney functions to be normal. There was no explanation from their side to what was going on. In the end, we had to stop the diet. Follow up confirmed persistently normal blood K levels.

The association of hypokalemia with the KD is well known. The mechanism might be due to the diuretic effect of the diet. This water loss is associated with other mineral losses. We noticed that quiet few numbers of our patients got hypokalemia ranging between mild and moderate. This necessitated supplementation of K. To hit two birds with one stone, we used to supply our meant patients with K citrate to avoid stone formation and to decrease possible ketotic acidosis, though not on routine basis [29,30].

Here we highlight the necessity of laboratory investigations to early detect any electrolyte disturbance and to treat any hypokalemia. We have no explanation as to why the above child did not respond and even showed paradoxical response to k supply.

A case with GRIN2 a mutation refractory to ASMs responded to KD

Three years old boy, known to have drug resistant epilepsy. His neonatal and family history was unremarkable. At the age of six months, he began to have focal seizures followed by secondarily generalization. He was started on CBZ and remained seizure free for a couple of months. At eight months of age, he presented with flexor spasms. He was treated initially with prednisolone, and VGB. Spasms were refractory to both.

Then he was tried on many ASMs including Rufinamide (Ruf), Clobazam (Clbz) and Valproic Acid (VPA). Ruf and VPA were discontinued due to lack of benefit.

He exhibited other seizures' semiology including atypical absence, atonic and tonic seizures. He was started on KD up to 3:1. After four weeks and on the first visit, the mother reported 50% seizure reduction. The diet ratio was increased to 3.5:1 with subsequent 90% seizure reduction. Investigations revealed a normal basic metabolic work up. Comprehensive epilepsy gene panel and mitochondrial DNA testing showed variant of uncertain significance in GRIN2A and

MO02SAM111ACREBBP. All these mutations were heterozygous, but the associated condition is autosomal dominant.

MRI confirmed an unremarkable study. Long-term EEG monitoring disclosed 12 seizures with generalized spike and waves followed by attenuation. Seven of these were electro-clinical. Repeated EEG after the diet therapy, showed improvement with just focal discharges in the right frontal region.

The N-Methyl-D-Aspartate (NMDA) receptor subunit 2A (GRIN2A) gene encodes Glutamate NMDA receptor subunit epsilon-1 [31-34]. This protein is found in the brain and spinal cord neurons, including the regions of the brain responsible for language [35-38].

More than 50 mutation types found in the GRIN2A gene were involved in many neurological diseases, including refractory epilepsy and language disorders [39-42]. They are known to cause refractory epilepsy as well [43,44].

Landau-Kleffner Syndrome (LKS), Continuous Spike and Wave during Slow Sleep (CSWSS), and atypical Rolandic Epilepsy (RE) were reported to be caused by de novo or inherited mutations in the GRIN2A gene [45-47].

The up to 20% patients with epileptic aphasia spectrum having mutations in the GRIN2A suggests that excitatory glutamate receptors play a key role in these disorders [48].

Treatment of epilepsy in such cases is difficult and many will need the change of many ASDs after trial failure of each.

Needless to mention intellectual disability, aphasia and the autistic spectrum in such cases are non-treatable. The use of KD in such cases is not widely published.

The mechanism by which the diet might have improved our patient seizures possibly lies between the different hypotheses that try to explain the mechanisms of actions of the diet. The child already received drugs that are sodium channel blockers (CBZ, VPA and Ruf). He also received VGB that is supposed to have an irreversible inhibition of Gama Amino Butyric Acid (GABA) -transaminase, in addition to his being on PB which is a chloride channel opener. The changes in intracellular-extracellular electrolyte ratios, correction of hypoglycemia or low intracellular glucose, reduction in cerebral water content, an anti-inflammatory action, and immune modulation or suppression are hypothesized mechanisms of action of steroids which the child has been on for some time.

The potentiation and increase of GABA was delivered by VPA and Clbz. He had the chance of selective enhancement of slow inactivation of voltage-gated sodium channels through Lacosamide (LCZ) that he is still on [49-51].

To explain the success of the diet, we may consider other mechanisms that KD is thought to have and are not shared by the previously mentioned drugs. Those include beliefs like chronic changes in hippocampal excitability [52], impairing energy metabolism. In the epileptogenic areas, or increasing Adenosine and decreasing Adenosine kinase [53]. We do not know which mechanism could hit the target of reducing the child's seizures and ameliorating their frequency and severity. But we report on this GRIN2A mutation case who impressively responded to the diet after failure of reputable ASMs.

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