American Journal of Medical Case Reports, 2015, Vol. 3, No. 4, 117-120
Available online at http://pubs.sciepub.com/ajmcr/3/4/9

DOI:10.12691/ajmcr-3-4-9

Gilbert's Syndrome Successfully Treated with the Paleolithic Ketogenic Diet

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Received March 17, 2015; Revised April 03, 2015; Accepted April 12, 2015

Abstract Gilbert's syndrome (GS) is a common hyperbilirubinaemia syndrome caused by reduced conjugation of serum bilirubin by the liver. Although it is considered as a common and harmless condition not requiring treatment symptoms associated with GS may be unfavorable. Here we present a case of GS where high level of total and direct bilirubin, yellowish discoloration of the sclera as well as associated symptoms including migraine, fatigue and granulomatosus dermatitis were reversed following a shift toward the popular paleolithic and then toward the paleolithic ketogenic diet.

Keywords: *Gilbert's syndrome, Paleolithic ketogenic diet, hyperbilirubinaemia, liver function*

Cite This Article: Csaba Tóth, and Zsófia Clemens, "Gilbert's Syndrome Successfully Treated with the Paleolithic Ketogenic Diet." *American Journal of Medical Case Reports*, vol. 3, no. 4 (2015): 117-120. doi: 10.12691/ajmcr-3-4-9.

1. Introduction

Gilbert's syndrome (GS) is a hereditary hyperbilirubinaemia syndrome affecting 5-10% of the population [1]. It is primarily attributed to impaired conjugation of bilirubin in the liver due to decreased bilirubin glucuronyltransferase activity. Impaired activity of this enzyme is attributed to mutations of the UGT1A1 gene. Beside this failure other alterations of the hepatic bilirubin metabolism have been suggested in GS including impaired hepatic uptake of bilirubin [2] and a positive feedback of bilirubin through its mild haemolytic effect [3].

GS is regarded as a common and harmless condition. In population studies GS is associated with decreased cardiovascular risk and all-cause mortality [4,5] which may also be due to to the low BMI of those with GS [3]. Nevertheless GS is also known to be associated with a set of unfavorable symptoms including fatigue, itching, gastrointestinal symptoms [2], increased risk for gallstones [6] as well as several unspecific symptoms including neurologic ones.

Given that GS is regarded as a chronic condition not requiring treatment symptoms are persisting life-long after onset of the disease. Herein we present a case of a patient with GS in whom both laboratory parameters and associated symptoms have been reversed following a shift toward the popular paleolithic and then toward the paleolithic ketogenic diet. Previously we have published successful treatment of epilepsy [7], type 1 diabetes [8] and metabolic syndrome [9] with the paleolithic ketogenic diet. This diet is close to the meat-fat based diet originally proposed by gastroenterologist Voegtlin as being the evolutionary adapted diet in humans [10].

2. Case Report

In 2006 GS was accidentally discovered in the female patient aged 30 due to a routine laboratory test. This showed elevations in both serum total bilirubin (31 µmol/l) and directbilirubin (9.16 µmol) levels. Liver function tests as well as other laboratory parameters were normal except for low serum iron concentration (Table 1). Sclera of the eyes showed persistent yellowish discolouration but no signs of liver disease were present. Based on the proportion of direct bilirubin to total bilirubin and clinical features the hyperbilirubinaemia was classified as Gilberts's syndrome [11]. At this time the patient had a 10-year history of migrain episodes with an average frequency of ~3/month. Her additional symptoms included fatigue, constipation and unclassified granulomatosus dermatitison both legs. Dermatitis was present for 10 years. No biopsy was taken to specify histology. She had not been taking any medicines, vitamins or other supplements. She reported no smoking and alcohol abstinence. She was weak with a BMI of 17,9 (weight: 50 kg, height: 167 cm).

2.1. Popular Paleolithic Diet

On 09 November 2010 the patient decided to initiate the paleolithic diet. Laboratory blood test performed at diet onset showed a further eleveation in total bilirubin but other laboratory parameters were normal (Figure 1 and Table 1). Direct bilirubin was not tested at this time. The popular form of the paleolithic diet she initiated restricted

milk, dairy, refined carbohydrates, cereals, legumes, maize, rice and most vegetable oils. Thus the diet was based on vegetables, fruits, meat, eggs but also contained oilseeds, coconut oil, sugar alcohols and coconut. This diet was however low in animal fat, red meats and offal. Amount of fat, protein and carbohydrates were not predefined in the popular paleolithic diet. She had been following the diet for 20 months between Nov 2010 and Jul 2012.

A laboratory test on 09 Nov 2011, a year after diet onset, indicated a decrease in the level of both total and direct bilirubin. Iron level was now in the normal range and other parameters were normal too (Table 1). Yellowish decoloration of the sclera disappeared. There was a decrease in the number of migraine episodes (~6 episodes/year) and constipation resolved too. However there was no change in feeling fatigue and in the presence of granulomatosus dermatitis. Another concern was weight loss. While on the popular paleolithic diet she lost 5 kilograms and so her BMI at this time was only 16.1.

2.2. Paleolithic Ketogenic Diet

In July 2012 we adviced a shift toward the paleolithic ketogenic diet. This diet is based on animal fat, meat, eggs and offal and to a lesser extent (less than 30%) vegetables and fruits. Fat to protein ratio was at least 2:1 (in gram). Fat and red meats derived from pork and cattle were encouraged over lean meats from poultry. She consumed offal from pork and cattle (predominantly liver, brain and marrow) at least two times a week. She was avoiding foods with additives including nitrites and/or nitrates. Foods that are allowed or even encouraged in the popular paleolithic diet such as artificial sweeteners, coconut oil, oilseeds, oilseed flours and cocoa were excluded. She used small amounts of honey. Ketosis was checked regularly by urinary keton strips which showed sustained ketosis. The four laboratory tests taken five months, 12 months, 19 months and 31 months after the onset of the paleolithic ketogenic diet showed total bilirubin and direct bilirubin levels below the upper reference limit (Figure 1). In these measurements cholesterol and LDL cholesterol were elevated but other laboratory measures were normal. Testing for folic acid, vitamin B12 and vitamin D (25(OH)D) in years 2014 and 2015 showed adequate levels of these vitamins (Table 1).

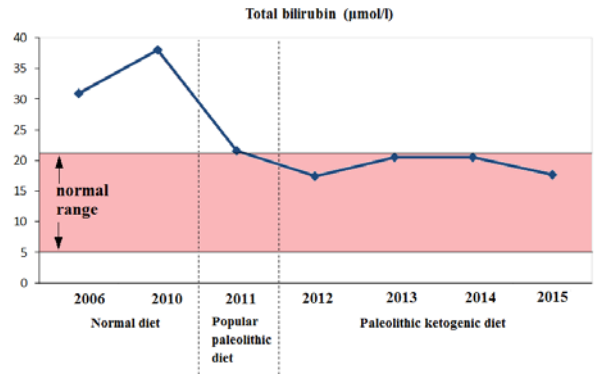

Figure 1. Time course of total bilirubin levels through the normal, the popular paleolithic and the paleolithic ketogenic diet. Note that with a shift toward the popular paleolithic and then toward the paleolithic ketogenic diet bilirubin levels fall below the upper reference limit

While on the paleolithic ketogenic diet her fatigue disappeared and she experienced increased fittness both physically and mentally. Her migraine episodes further decreased (to ~2/year). Granulomatosus dermatitis disappeared on both legs. Her weight was increased by 4 kilograms. Currently her BMI is 17.6. She reports no side effects of the diet.

3. Discussion

GS is regarded as a lifelong condition of altered bilirubin metabolism [11]. In our patient, however, clinical features designating this condition have been reversed by shifting first toward the paleolithic then toward the paleolithic ketogenic diet. During this time serum level of both total and directbilirubin declined below the upper limit of the normal range. Although bilirubin levels decreased and yellowish decoloration of the sclera disappeared while on the popular paleolithic diet, weakness, fatigue, migraine and granulomatosus dermatitis improved considerably only after the shift toward the paleolithic ketogenic diet.

While on the paleolithic ketogenic diet a laboratory assessement indicated low level of inflammatory markers (CRP, fibrinogen), normal level of triglicerides, uric acid, glucose, ions, normal liver and kidney function. Total cholesterol as well as LDL cholesterol were elevated. Such a laboratory profile corresponds to that seen in our previous patients with epilepsy [7], type 1 diabetes [8] and metabolic syndrome [9] on the paleolithic ketogenic diet. Supplementing vitamins on the classical ketogenic diet is generally recommended. In the present case, however, despite the absence of supplementing, vitamin D, folic acid and vitamin B12, as assessed by laboratory measurements in 2014 and 2015, were in the normal range.

Physicians generally opine that a metabolic condition with a perceived genetic predisposition such as the GS cannot be influenced by diet. We are not aware of studies using dietary intervention is GS. However fasting and glucose administration both orally and intravenously are known to elevate bilirubin levels in GS patients [12,13]. Interestingly in a study carried out 40 years ago both phenomena could be reversed by the addition of lipids [14]. Then it was concluded that both phenomena are due to the withdrawal of lipids.

Current dietary guidelines recommend the reduction of fat and especially saturated fat in the diet [15]. However there is growing evidence that the recommendation on high carbohydrate/low fat diet may not be supported with sufficient evidence [16] while carbohydrate-restricted ketogenic diets have been shown to confer several health benefits [17]. This was also the case in our patient with GS and in the three other cases on the paleolithic ketogenic diet [7,8,9].

It is of important to emphasize that unlike the classical ketogenic diet which is known to be associated with several adverse effects the paleolithic ketogenic diet does not have any side effects as also examplified our present and previous patients [7,8,9]. A second important point is that although in this case there were some improvements onthe popular paleolithic diet, the remaining symptoms were only resolved with the paleolithic ketogenic diet.

We believe that the beneficial effects of the paleolithic ketogenic effect are due tothe shift from carbohydrate-based to fat-based metabolism, adequate intake and bioavailability of vitamins and minerals as well as the restriction of ”antinutrients” found in non-paleolithic [18] and in the popular paleolithic foods.

In the literature there are a few short-term studies [19,20,21] and a long-term intervention study [22] with the paleolithic diet in healthy people and in patients with metabolic syndrome. The present case strenghtens our experience that the paleolithic diet in its widely used popular form is limited in effectiveness in diseases with components other than glucose metabolism alterations. The paleolithic ketogenic diet, however, may be remedial in these cases [7,8,9,23].

Table 1. Laboratory data while on the normal, the popular paleolithic and the paleolithic ketogenic diet. Dashes indicate that the given parameter was not measured

	Normal diet		Popular paleolithic diet	Paleolithic ketogenic diet				
	26 Apr 2006	09 Nov 2010	09 Nov 2011	04 Dec 2012	18 Jul 2013	11 Feb 2014	12 Feb 2015	
Total bilirubin	31	38	21.6	17.4	20.5	20.5	17.7	µmol/l
Direct bilirubin	9.16	-	< 5	-	-	3	3	µmol/l
WBC	8.6	5.9	6.3	6.06	6.1	6.4	6.4	G/l
RBC	5.07	4.02	4.78	4.44	4.82	4.8	4.6	T/l
Hgb	143	124	139	136	141	144	136	g/l
Ht	45	38	43	41	42	0.44	0.42	%
Thrombocyte	277	242	285	284	249	253	252	G/l
Natrium	136.3	138	138	132	133	136	138	mmol/l
Kalium	3.8	4	4.3	4.1	4.4	4.2	4.1	mmol/l
Glucose	4.7	4.8	5.1	5.1	5.5	5.4	4.7	mmol/l
GGT	10	15	13	16	19	14	13	U/l
GOT	19	11	16	12	15	20	22	U/l
GPT	26	22	26	23	33	15	12	U/l
ALP	70	55	70	62	66	-	-	U/l
Total cholesterol	4.03	-	4.8	5.8	5	7.7	6.8	mmol/l
HDL cholesterol	1.95	-	2.25	2.23	2.36	-	2.21	mmol/l
LDL cholesterol	1.81	-	2.39	-	-	-	4.49	mmol/l
Triglycerides	0.59	-	0.35	0.48	0.24	0.71	0.99	mmol/l
Uric acid	189	-	-	188	175	201	266	µmol/l
Total protein	79.3	72	70	72	71	73	72	g/l
Albumin	50	42	49	40	40	47.8	48.2	g/l
Carbamide	3.8	4.5	4.1	5	4.7	5.7	5.7	mmol/l
Creatinine	72	89	68	58	79	63	75	µmol/l
CRP	<3	1	1	1	<3	0.27	0.28	mg/l
ESR	-	-	3	7	3	3	4	mm/h
Iron	8.2	-	17.6	14.9	24.9	22.1	19.7	µmol/l
Magnesium	-	-	-	-	0.64	0.87	0.84	mmol/l
Vitamin B12	-	-	-	-	-	371.6	429	pmol/l
Folic acid	-	-	-	-	-	51.2	31.8	nmol/l
25(OH)D	-	-	-	-	-	163	124.1	nmol/l

Abbreviations: WBC – white blood cell, RBC – red blood cell, Hgb – hemoglobin, Ht – hematocrit, GOT – glutamate-oxaloacetate transaminase, GPT – glutamate-pyruvate transaminase, GGT – gamma-glutamyl transferase, ALP – alkaline phosphatase, CRP – C reactive protein, ESR – erythrocyte sedimantation rate.

Funding

None

Statement of Competing Interests

The authors have no competing interests.

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