Review

DOI: 10.5582/irdr.2017.01040

Management of syndromic diarrhea/tricho-hepato-enteric syndrome: A review of the literature

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Summary **Syndromic diarrhea/tricho-hepato-enteric syndrome (SD/THE) is a rare disease linked to the loss of function of either TTC37 or SKIV2L, two components of the SKI complex. It is characterized by a combination of 9 signs (intractable diarrhea, hair abnormalities, facial dysmorphism, immune abnormalities, IUGR/SGA, liver abnormalities, skin abnormalities, congenital heart defect and platelet abnormalities). We present a comprehensive review of the management of SD/THE and tested therapeutic regimens. A review of the literature was conducted in May 2017: 29 articles and 2 abstracts were included describing a total of 80 patients, of which 40 presented with mutations of *TTC37*, 14 of *SKIV2L*. Parenteral nutrition was used in the management of 83% of the patients and weaned in 44% (mean duration of 14.97 months). Immunoglobulins were used in 33 patients, but data on efficacy was reported for 6 patients with a diminution of infection (*n* = 3) or diarrhea reduction (*n* = 2). Antibiotics (*n* = 11) provided no efficacy. Steroids (*n* = 17) and immunosuppressant drugs (*n* = 13) were used with little efficacy and mostly in patients with IBD-like SD/THE. Hematopoietic stem cell transplantation (HSCT) was performed in 4 patients: 2 died, for one it corrected the immune defects but not the other features and for the last one, it provided only a partial improvement. Finally, no specific diet was effective except for some contradictory reports for elemental formula. In conclusion, the management of SD/THE mainly involves parenteral nutrition and immunoglobulin supplementation. Antibiotics, steroids, immunosuppressants, and HSCT are not recommended as principle treatments since there is no evidence of efficacy.**

Keywords: TTC37, SKIV2L, very early onset IBD

1. Introduction

Syndromic diarrhea/tricho-hepato-enteric syndrome (SD/THE) is a rare disease linked to an alteration of the human SKI complex by recessive mutations of either *TTC37* or *SKI2VL*. To date, it is characterized by the combination of 9 signs (*1*). As nearly constant features are found intractable diarrhea during infancy, hair abnormalities often found with presence of trichorrhexis nodosa, intra-uterine growth restriction or small size at birth for gestational age, facial dysmorphism, immune abnormalities (mostly a lack of immunoglobulin or a lack of antibody response to vaccination). The other signs seen in half of the cases are liver abnormalities, and skin abnormalities but congenital heart defects and platelet abnormalities are not often reported (*1-2*). To date case management involves parenteral nutrition and in some cases immunoglobulin supplementation (*1*). However, a lot of empirical treatments have been tried over the past 30 years because of delayed diagnosis. The aim of this review is to assess these treatments and their potential efficacy.

Released online in J-STAGE as advance publication August 19, 2017.

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Table 1. Summary of clinical signs according to molecular defect

Items	All (*n* = 80)	Patient with mutation of TTC37 (*n* = 40)	Patient with mutation of SKIV2L (*n* = 14)	Patient not tested (*n* = 25)	Patient without mutation of SKIV2L or TTC37 (*n* = 1)
Sex (F/M)	39/35	20/18	8/5	11/11	0/1
Intractable diarrhea	76/77	38/39	14/14	23/23	1/1
Facial dysmorphism	66/67	31/32	10/10	24/24	1/1
Hair abnormalities	71/73	36/36	11/13	23/23	1/1
Trichorrhexis nodosa	46/59	30/32	5/13	11/14	
Immune deficiency	48/67	28/36	5/12	15/18	0/1
IUGR/SGA	48/63	24/32	9/9	15/21	0/1
Liver disease	41/61	18/31	8/10	14/19	1/1
Skin abnormalities	29/48	15/24	6/6	8/17	0/1
Hypo/hyperpigmented	17/29	12/15	4/6	1/8	
Cardiac abnormalities	15/43	10/26	4/4	1/13	
Outcome (Alive/Dead)	56/24	30/10	13/1	12/13	1/0

2. Methods

A search was done on PubMed (*www.pubmed.com*) in May 2017 using "trichohepatoenteric", "tricho-hepato-enteric", "intractable diarrhea with phenotypic anomalies", "intractable diarrhea and trichorrhexis nodosa" , "syndromic diarrhea", "syndromic diarrhoea" and "phenotypic diarrhea", "stankler syndrome", "SKIV2L" and "TTC37". All in all, we retrieved 73 articles of which 27 had individual clinical data (*3-29*). A second search on Google scholar (*www.scholar.google.fr*) in the "cited by" article from Girault *et al*. (*4*) and Verloes *et al*. (*5*), produced 2 more articles (*30-31*). A search performed on abstracts from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) meetings from 2012 to 2017, produced two abstracts with unpublished data (*32,33*). Finally, a medical thesis provided more complete clinical data from patients that were only briefly described in reference 11 (*34*). Consequently, 29 articles, 2 abstracts and 1 medical thesis were included. For each case the clinical data (regarding the 9 canonical signs), genetic status, disease evolution, treatments and their efficacy were retrieved. Statistical analyses were performed with biostatgv software.

3. Results

3.1. *Clinical data*

Between 1982 and May 2017, 80 patients (sex ratio 35/39 for patients with recorded sex) were described as having SD/THE with some clinical data. 14 presented disease with variants in SKIV2L, 40 in TTC37, 25 were of unknown status and 1 was negative for both TTC37 and SKIV2L. The patients presented classical SD/THE symptomatology with nearly all (> 97%) presenting with intractable diarrhea, facial dysmorphism and hair abnormalities. More than 2/3 were small for gestational age, presented an immune deficiency or liver disease.

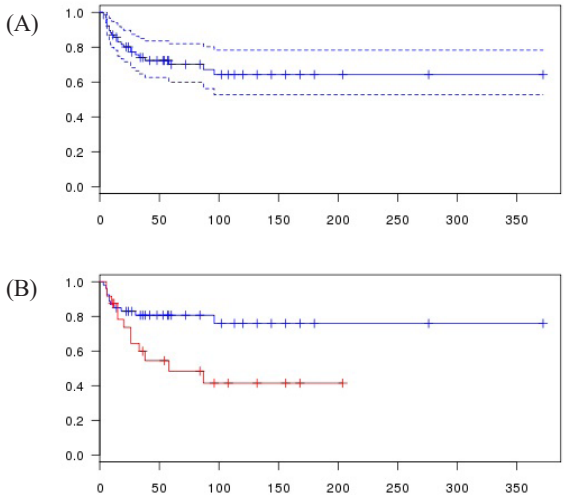

Figure 1. Kaplan-Meier survival curve. (A), whole cohort (dashed line 95% confidence Interval); **(B)**, According to genetic status (mutated in SKIV2L or TTC37 in blue, Unknown in red); $p = 0.019$. Time in month

Skin abnormalities (60%) and cardiac abnormalities (35%) were the least recorded signs. One third of the patients died at a mean age of 23.5 months (3-96), mostly, from infection (7 patients) or hepatic failure (7 patients) for the 18 patients with recorded information. The probability of survival for the whole cohort at 96 months was 0.64 (± 0.06) and 0.76 (± 0.07) for patients mutated in SKIV2L or TTC37 respectively, or 0.41 (± 0.11) for patients of unknown status at 87 months ($p = 0.019$). Table 1 summarizes the clinical data according to molecular defect. Figure 1 shows the Kaplan-Meier survival curve for the whole group of patients and compares patients according to their molecular status.

3.2. *Therapeutics*

Table 2 and 3 summarizes the therapeutic and dietetic management for the 80 patients according to molecular defect. A detailed account is given in the following paragraphs.

3.2.1. *Nutritional management*

Parenteral nutrition was used in 83% of the patients. Nearly half had been weaned off parenteral nutrition with a mean duration of 14.97 months (1-55). However, non-weaned patients stayed on parenteral nutrition for a long period of time (Figure 2).

3.2.2. *Immunoglobulin supplementation*

Thirty three patients were given immunoglobulin supplementation, but the effects were described in only 6 cases. Three reported a diminution of infection (*4,19,21*), 2 a reduction of diarrhea (*4,23*) and 1 described no effect either on diarrhea or infection (*34*).

3.2.3. *Antibiotherapy*

In 11 cases, antibiotics were used to treat SD/THE, mostly in Girault *et al*. (8 patients with Vancomycin, Colistimethate, Tobramycin, and Amphotericin B) but also in Busoni *et al*. (Vancomycin, Amoxiciline, Metronidazole, Quinolone) and in Lee *et al*. 2016 (Ceftriaxone, Amikacine and "aggressive antibiotics") (*4,23,27*). In 10 cases (*4,23*) antibiotics had no effect and only in one case (*27*) lead to a temporary reduction in diarrhea.

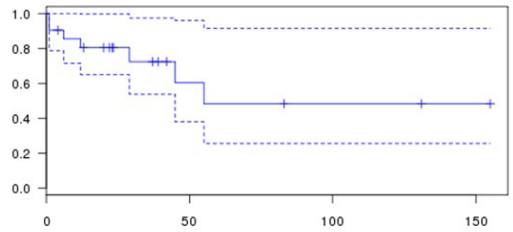

Figure 2. Kaplan-Meier survival curve of parenteral dependency according to the duration of parenteral nutrition (dashed line 95% confidence Interval). Time in month

3.2.4. *Steroids*

Steroids were administered to 17 patients (*4,17,23,26,27, 30,32-34*). No effect was reported in 11 patients and in 5 patients only a partial amelioration was noted. In one patient (*33*) there were no details and it was before HSCT. It should be noted that the patients with partial effect presented with some aspect of IBD-like SD/THE (*17,26,27,32*). In some cases steroids were given in combination with immunosuppressant drugs.

3.2.5. *Immunosuppressant drugs*

Seven drugs were used for a combined total of 24 times in 13 patients (*4,17,26,27,30,32,33*). Thus, some patients were given multiple drugs, either sequentially or at the same time. Summing up: 5 ASA was used four times with no effect in three patients (*17,27*) and one case of partial amelioration in combination with steroids (*27*). Azathioprine was used 5 times, with no effect in 4 patients (*4,17,26*) and possibly a partial amelioration in one (*26*). Ciclosporine was used in two patients in combination with steroids: one patient died of infection (*30*) and the other showed only a mild improvement (*4*). Methotrexate was used in one patient (*17*) with no effect. Sirolimus was used in 2 patients without effect, Tacrolimus was used twice in 3 patients without any effect (*17,26*) and one before HSCT (*33*). Anti-TNF antibody was used in 7 patients; for one there was no description of outcome (*33*), for 2 (*17*) there was no improvement, for 3 there was a partial and inconsistant improvement (*26,27,32*).

Table 2. Summary of therapeutic management according to molecular defect

Items	All (n = 80)	Patient with mutation of TTC37 (n = 40)	Patient with mutation of SKIV2L (n = 14)	Patient not tested (n = 25)	Patient without mutation of SKIV2L or TTC37 (n = 1)
Parenteral nutrition	59/71	29/34	11/13	18/23	1/1
Weaning of parenteral nutrition	22/50	10/23	5/9	6/17	1/1
Mean duration in month of parenteral nutrition for weaned patients	14.97 (1-55)	12.6 (1-29)	10.62 (4-24)	25 (1-55)	6
Mean duration in month of parenteral nutrition for ongoing patients	57.09 (4-179)	67.94 (13-55)	105.33 (66-179)	32.85 (4-155)	6
Immunoglobulin supplementation	33/40	19/22	3/5	11/12	0/1
Azathioprine	5	2	2	1	0
Methotrexate	1	1	0	0	0
Ciclosporine	2	0	0	2	0
Sirolimus	2	1	1		
Tacrolimus	3	2	1	0	0
Steroids	17	9	2	6	0
TNF blockade	7	5	2	0	0
Antibiotics	11	3	0	8	0
5 ASA	4	3	1	0	0
Hematopoietic stem cell transplantation	4	3	0	1	0

Table 3. Summary of diet management according to molecular defect

Items	All (*n* = 80)	Patient with mutation of TTC37 (*n* = 40)	Patient with mutation of SKIV2L (*n* = 14)	Patient not tested (*n* = 25)	Patient without mutation of SKIV2L or TTC37 (*n* = 1)
Elemental formula	7	2	2	2	1
Lactose free diet	3	2	1	0	0
Glucose-Galactose free diet	3	1	0	1	1
Gluten free diet	4	1	0	2	1
Hydrolyzed formula	11	4	1	5	1

Eight patients on immunosuppressive therapy were described as having an IBD-like SD/THE. Moreover, patients described in Kammermeier 2014 and 2017 (*17,26*) were given multiple immunosuppressant drugs (2 patients treated with 2 molecules, and 2 patients with 5). For these patients, reported in a synthetic table, it is rather hard to determine the efficacy of each therapy precisely.

3.2.6. *Hematopoietic stem cell transplantation (HSCT)*

HSCT was performed on 4 patients. The first one was in Girault *et al*., and the patient underwent two HSCT: the first was a failure and he died from severe interstitial pneumonia after the second attempt (*4*). Another case was reported in Kammermeier *et al*.: HSCT produced only a moderate improvement, however the case is very slightly reported (*26*). Two patients were reported in Cleminson *et al*.: one died, 46 days post HSCT, from adenovirus pneumonitis, the second reported successful engraftment and after nearly two years of follow-up, immunology normalized afterwards but diarrhea and failure to thrive persisted (*33*).

3.2.7. *Diet management*

For 22 patients, some information about diet was available (Table 3). 11 were given hydrolyzed formula, 7 an elemental formula, 4 a gluten free diet and 3 a lactose free diet and 3 a glucose-galactose free diet. Except for elemental formula which led to an amelioration of the diarrhea for 2 patients (*21,24*), all other types of diet did not improve the diarrhea. For one patient, both soy based formula and artisanal rice water with sugar cane were provided, but did not improve diarrhea (*30*).

Of the twelve patients who were not given parenteral nutrition, one was reported to have a normal diet (*24*) and one was given hydrolyzed formula (*32*). There is no data of the diet for the others. For the 22 patients weaned off parenteral nutrition, data are available about the diet for 11. Five patients were given elemental formula and/or gluten free and cow's-milk-free diets (*18*). All the others were given a different diet: no gluten or cow's milk (*4*), hydrolyzed formula (*4*), elemental formula (*24*), or a hydrolyzed formula, gluten free diversified diet (*11,34*), or normal diet with enteral supplement (*24*) or glucose galactose free formula (*31*).

4. Discussion

As far as we know, this is the first comprehensive review of the management of SD/THE. Up to now, no clinical trials have been organized, only single cases or small series are reported with only a low level of evidence. However, some elements can be highlighted. We confirm that parenteral nutrition is important in the management of SD/THE as already established in previous reviews (*1,11*). It also plays a vital role in the management of SD/THE, since 83% of the patients need it. However, there is some variability and 17% of the patients did not require parenteral nutrition. Except for some cases (*19,24*), it is not clear whether the absence of parenteral nutrition was due to non-availability or for some other reason. With parenteral nutrition, weaning can be achieved in nearly 50% of the patients as already reported in the literature (*35*). One of the limits with this approach is that it can also reflect different practices in different countries. Moreover, it often remains unclear if weaned patients have a good nutritional status or if some level of parenteral nutrition may still be useful. It has already been noted that SD/THE patients are of small stature despite adequate nutrition (*11,35*) and that in two patients growth hormone administration failed to improve growth (*35*).

Immunoglobulin supplementation was used in 33 patients, but the effects are rarely and poorly described. Nonetheless, an improvement of either the number of infections or of the diarrhea was noticed for 5/6 patients. Thus, immunoglobulin supplementation could probably be useful in some cases of SD/THE if an immune defect is present (notably low levels of immunoglobulin), but also in case of recurrent infection, as we know that immunoglobulin function is impaired (*19*). In all cases a discussion with immunologists appears mandatory.

Steroids, antibiotics or immunosuppressant drugs did not seem useful in the management of SD/THE and can even have adverse effects. The only exception is in IDB-Like SD/THE, where these drugs could be useful to some extent. However, as noted in Busoni *et al*., the effect seems transient or partial (*27*).

Hematopoietic stem cell transplantation presents only little data with no full reports. However according to the data, HSCT did not cure SD/THE, except possibly for the immune defects, but is associated with high mortality (2/4). Thus SD/THE is clearly different from

defects in intestinal immune-related homeostasis like immunodysregulation polyendocrinopathy enteropathy, X-linked (IPEX) or IPEX-like disorders where either immunosuppressant drugs or HSCT could be useful (*36*).

For diet management, data are hard to come by and the only regimen that seems to have some effect is the elemental formula, and even then reports are contradictory. All the others did not seem to be effective. The diet of weaned patients is highly diverse thus it is hard to determine whether restrictive diets (like gluten, lactose, cow's milk free) are really useful. No suggestion can be made on the basis of the data and the choice should be made by the medical team in agreement with the patient and the family.

On a more general level, mortality is still high for SD/THE. Whereas, mortality is lower for patients with mutation of TTC37 or SKIV2L than for patients with unknown status. However, these cases could be a bias because most of the patients with unknown status are from older publications.

In conclusion, to date the management of SD/THE is mainly based on parenteral nutrition and immunoglobulin supplementation. Other drugs such as antibiotics, steroids and immunosuppressant drugs have, showed no evidence of efficacy, except in some cases of IBD-like SD/THE. HSCT could potentially treat the immune defects but does not improve the other signs and is associated with high mortality. Finally, diet management data are confusing and no clear conclusion can be made. SD/THE is a rare disease requiring management by an expert team, especially in relation to nutrition and immunity.

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(Received July 18, 2017; Revised July 27, 2017; Accepted August 11, 2017)