Molecular Genetics and Metabolism Reports 11 (2017) 8–11

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Chronic intestinal pseudo-obstruction. Did you search for lysosomal storage diseases?

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ARTICLE INFO

Article history:
Received 19 March 2017
Accepted 19 March 2017
Available online 25 March 2017

Keywords:
Fabry disease
Lysosomal storage disease
Sphingolipidoses

ABSTRACT

Chronic intestinal pseudo-obstruction results in clinical manifestations that resemble intestinal obstruction but in the absence of any physical obstructive process. Fabry disease is an X-linked lysosomal storage disease characterized by the dysfunction of multiple systems, including significant gastrointestinal involvement. We report the occurrence of chronic intestinal pseudo-obstruction in two unrelated patients with Fabry disease and the possible explanation of a direct relation of these two disorders. In Fabry disease, gastrointestinal symptoms occur in approximately 70% of male patients, but the frequency ranges from 19% to 69% in different series. In some patients, colonic dysmotility due glycolipid deposition in autonomic plexus and ganglia can lead to the pseudo-obstruction syndrome, simulating intestinal necrosis. That is why up to this date colostomy has been performed in some cases, even for children with FD without cardiac, renal or cerebrovascular compromise. Early treatment with enzyme replacement therapy in asymptomatic or mildly symptomatic patients may be justified in order to prevent disease progression. Several studies have demonstrated that enzyme replacement therapy alleviates GI manifestations. Because of the non-specific nature of the gastrointestinal symptoms, diagnosis of Fabry disease is often delayed for several years. Gastrointestinal involvement is often misdiagnosed or under-reported. It is therefore very important to consider Fabry disease in the differential diagnosis of chronic intestinal pseudo-obstruction.

1. Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a high-morbidity syndrome that develops as a consequence of altered intestinal motility, which results in clinical manifestations that resemble intestinal obstruction but in the absence of any physical obstructive process [1]. CIPO is one of the most important causes of chronic intestinal failure both in pediatric (15%) and adult cases (20%), since affected individuals are often unable to maintain normal body weight and/or normal oral nutrition [2,3]. The severity of the clinical picture, generally characterized by disabling digestive symptoms even between sub-occlusive episodes, contributes to deterioration of quality of life of the patients. Furthermore, CIPO often passes unrecognized for long periods of time, so that patients almost invariably undergo repeated, unnecessary and potentially invasive surgical procedures [1]. Fabry disease (FD) is an X-linked lysosomal storage disease characterized by the dysfunction of multiple systems, including significant gastrointestinal (GI) involvement such as diarrhea, abdominal pain, early satiety and nausea [4]. The deficiency in lysosomal α-Gal A causes accumulation of globotriaosylceramide (GL-3) within the lysosomes of multiple cell types throughout the body. This accumulation results in inflammation, ischemia, hypertrophy, and the development of fibrosis ultimately resulting in cellular damage and progressive organ dysfunction [5,6]. Although FD was thought to be rare, only affecting 1 in 40,000; recent newborn screening data show it to be much more common, affecting up to 1 in 3400–4000 newborns [7].

2. Aim

We report the occurrence of CIPO in two unrelated patients with Fabry disease and the possible explanation of a direct relation of these two disorders.

3. Cases report

Case 1: 62 years old female with classic phenotype of FD (mutation: A292T). At her initial visit for FD at the age of 59, the patient described isolated bloating and sporadic diarrhea with intermittent abdominal colic pain since the age of 18. Medical records showed at least 4 hospitalizations for intestinal pseudo-obstruction during the last 20 years.

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http://dx.doi.org/10.1016/j.ymgmr.2017.03.004

Ophthalmologic exam showed cornea verticillata. She had echocardiographic evidence of left ventricular hypertrophy (LVH) and had a history of arrhythmias. Brain MRI showed ischemic periventricular lesions. Laboratory exam showed microalbuminuria with normal estimated glomerular filtration rate (eGFR). She presented with a 5-day history of abdominal pain, primarily in the right lower quadrant and associated with intermittent fevers. Abdominal CT reported distended bowel loops, thickening of the proximal colon wall and free fluid in adjoining fascias. The following day, physical exam revealed an absence of abdominal sounds and progressively worsening pain. The patient underwent abdominal surgery with right colonic resection and placement of colostomy due a suspicion of tumoral obstruction. Pathological findings in H&E stained paraffin sections demonstrated enlarged ganglion cells with foamy cytoplasm present within Meissner's plexus of the submucosa present in the ileocecal valve sample. The foamy appearance likely represented the presence of GL-3 accumulation, lost in the paraffin processing. Epoxy resin sections taken from this same area show enlarged ganglion cells filled with zebra bodies, further suggesting the accumulation of GL-3. Ganglion cells of Auerbach's plexus present between the two muscular layers of the muscularis propria were also engorged with GL-3 accumulation (Fig. 1a). Substrate accumulation was also present in the smooth muscle cells of small arteries present in the submucosa (Fig. 1b), and within smooth muscle myocytes of the muscularis propria.

Case 2: 37 years old male patient was diagnosed with classic FD (mutation: D155H) following a renal biopsy for proteinuria study. The patient had other classic symptoms of FD including chronic abdominal pain and episodes of diarrhea during childhood, neuropathic pain in the hands and feet associated with fever and exercise, angiokeratomas and cornea verticillata. Furthermore, echocardiogram showed mild LVH and brain MRI showed small periventricular ischemic lesions. At the age of 32, the patient was hospitalized due abdominal pain and diverticulitis; after 2 days of conservative treatment he made a full recovery. At the age of 38, the patient developed fever and progressive left, lower-quadrant abdominal pain. After 3 days of conservative treatment, physical exam revealed severe abdominal distention, absence of abdominal sounds and progressively worsening pain. Abdominal surgery showed sigmoid colon distention and a delustered appearance; bowel resection with placement of colostomy was performed. Pathological examination of H&E stained paraffin revealed neither obstructive process nor inflammatory infiltration. Enlarged and vacuolated neurons in the Meissner's and Auerbach's plexuses (Fig. 2a) and intracellular inclusions in the smooth muscle cells of small arteries were present in the submucosa. Some vessels were narrowed and a few were occluded at this level (Fig. 2b).

Discussion

CIPO may be primary, when it exclusively involves intestinal smooth muscle or enteric neural plexus, or secondary to other conditions. The histopathologic presentation of CIPO can be divided in neuropathic, mesenchymopathic and myopathic forms based on abnormalities affecting the integrity of nerve pathways supplying the gut (either intrinsic or extrinsic), interstitial cells of Cajal (ICC) or smooth muscle cells, respectively. Table 1. Neuropathic, mesenchymopathic and myopathic changes may contribute to gut dysmotility either individually or in combination (e.g. neuro-myopathies or neuro-ICC alterations) [8].

In FD, gastrointestinal symptoms occur in approximately 70% of male patients [4,5], but the frequency ranges from 19% to 69% in different series [9,10]. In heterozygous patients (females) almost half of them may experience GI symptoms and some of those symptoms, such as constipation, are reported almost twice as often by female patients as by male patients [11].

Significant GI involvement has also been observed in children and can progress in severity with age. In a systematic review, Laney and colleagues observed that GI symptoms even presented in very young children, aged 1–4 years old, most commonly complaining of abdominal pain [12]. The symptoms present soon after the development of acroparesthesias and can be the initial symptom of FD in up to 20% of patients [13]. Abdominal pain is described as cramping mid-abdominal discomfort, frequently worsened with meals and increased stress. The possible local ischemia due endothelial deposits of GL-3 has led to the suspicion of 'intestinal angina' being the cause for post-prandial abdominal pain in some patients.

The second most common symptom is diarrhea occurring in 20% of patients [14]. The diarrhea can be intake-triggered, frequently associated with significant urgency and frequency, and occurring up to 15 times daily. Some patients report severe urgency leading to routine fecal incontinence. In some patients, colonic dysmotility can lead to the pseudo-obstruction syndrome, simulating intestinal necrosis. That is why up to this date colostomy has been performed in some cases [11,15], even for children with FD without cardiac, renal or cerebrovascular compromise. Intestinal perforation, secondary to diverticular disease, has been repeatedly described in the literature. The location of diverticula has been described as occurring at the duodenal, jejunal, and colonic levels [15–17].

Neuropathic pain (acroparesthesias) and GI involvement may be explained due a multifactorial cascade. Substrate deposits of GL-3 in autonomic ganglia (dorsal root ganglia -DRG- and myenteric and submucosal ganglia) may be the cellular alteration which results in the appearance of symptoms [18–22]. Intestinal ischaemia due

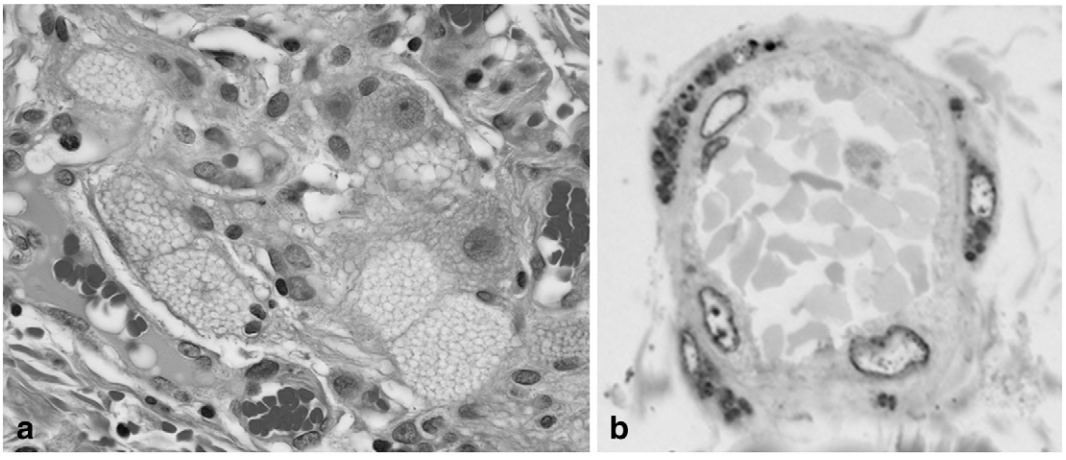

Fig. 1. a: Ganglion cells of Auerbach's plexus: Ganglion cells appear markedly foamy due to the accumulation of GL-3 (paraffin section, H&E, 600×). b: Vascular smooth muscle cells of submucosal arteries contain GL-3 (arrow). (HRLM, 1 μm epoxy resin, 1:1 Richardson's stain, 1000×).

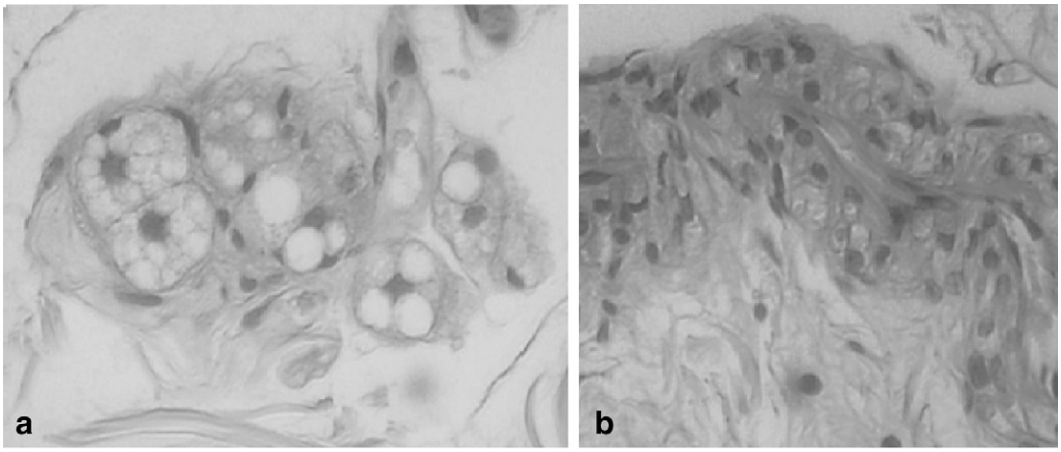

Fig. 2. a: Vacuolated cytoplasm of submucosal and myenteric plexus colon cells. (paraffin section, H&E, 600×). b: Vascular arterial lumen narrowing due smooth muscle cells vacuolated cytoplasm. (paraffin section, H&E, 600).

myenteric vessel occlusion could also be correlated with the small fiber neuropathy as a result of vasa nervorum obliteration [4]. Animal models with FD showed mechanical hypersensitivity in the von- Frey test and mechanical allodynia when compared with controls [23,24]. The same studies demonstrated that tissue involvement in DRG and small nerve fiber loss are linked with upregulation of sodium channels type 1.8 ($Na_v1.8$) and transient receptor potential vanilloid type 1 (TRPV1). The upregulation of these channels in DRG neurons causes an early depolarization of the resting potential, reduced threshold and increased frequency for evoked firing in these neurons, and increased fraction of DRG neurons that fire spontaneously. The GI manifestations reported by patients with FD might be explained by the effect of the GL-3 deposits on visceral afferents that are known to express $Na_v1.8$ and TRVP1 channels [25]. A specific role for $Na_v1.8$ in regulating gastrointestinal function is supported by experimental evidence showing that this channel (as well as $Na_v1.9$ also) is important for responses to mechanical stimulation and mechanical hypersensitivity of visceral afferents innervating the colon when challenged by an inflammatory mediators or food intake [25]. This hypothesis should be confirmed in further studies.

Enzyme replacement therapy (ERT) should be initiated in all affected patients with FD as soon as clinical signs and symptoms are observed. Early treatment of asymptomatic or mildly symptomatic patients may be justified in order to prevent disease progression [26]. Several studies have demonstrated that ERT alleviates GI manifestations [27–29]. This may be explained by a decrease of GL-3 accumulation in the endothelium of the intestinal vessels and by improved mesenteric circulation. ERT is presently available in the form of agalsidase alfa (Replagal®, Shire HGT, Inc., Cambridge, MA, USA) and agalsidase beta (Fabrazyme®, Sanofi Genzyme, Cambridge, MA, USA) [30,31]. Agalsidase alfa is given at 0.2 mg/kg body weight every other week by intravenous (IV) infusion and is approved in many countries throughout the world, though not by

Table 1
Causes of chronic intestinal pseudo-obstruction syndrome.

Myopathic		Neuropathic	Mesenchymopathic
Visceral	Mitochondrial	Central:	Loss of interstitial cells of Cajal
		• Parkinson disease • Multiple system atrophy • Stroke • Encephalitis • Tumor	
Primary:	Diseases from defective genes coding for proteins indirectly related to oxidative phosphorylation	Peripheral:	
• Absence of or selective decrease in smooth-muscle alpha-actin • Familial or sporadic visceral myopathy • Myopathy from abnormal gut morphogenesis • Autoimmune leiomyositis		• Diabetic neuropathy • Neuropathies potentially involving the enteric nervous system: Amyloidosis Hirschsprung Chagas Paraneoplastic syndromes Autoimmune diseases	
Secondary:	Diseases from genetically-induced mitochondrial DNA stability disturbance		
• Lupus, Polymyositis • Amyloidosis Ceroidosis (vitamin E deficiency) • Progressive muscular dystrophy, • Drugs (neuroleptics)			
	Diseases from defective nuclear genes coding for CRM enzyme complex proteins		

the USA Food and Drug Administration [32]. Agalsidase beta is administered at 1.0 mg/kg body weight once every 2 weeks as an IV infusion and is approved in Europe, the USA and many other countries.

There are no adequately powered head-to head studies that have compared the long-term effectiveness of the two enzyme preparations on clinical outcomes in well-characterized, phenotypically homogenous populations but evidence suggests that a higher agalsidase dose may be of clinical benefit in reducing GL-3 accumulation [33,34]. Because of the shortage of agalsidase-beta in 2009, many patients with FD were treated with lower doses or were switched from agalsidase beta to agalsidase alfa. One observational study assessed end-organ damage and clinical symptoms during dose reduction or switch from agalsidase beta to alfa. After 1 year, severity score index and frequencies of pain attacks, chronic pain, gastrointestinal pain, and diarrhea increased significantly in the dose-reduction and switch groups [35].

Because of the non-specific nature of the GI symptoms, diagnosis of FD is often delayed for several years. Gastrointestinal involvement is often misdiagnosed (usually as irritable bowel disease, visceral myopathy or inflammatory bowel disease) or under-reported. It is therefore very important to consider FD in the differential diagnosis of CIPO.

Conflict of interest statement

Juan Politei has received speaker honorarium from Genzyme, Shire and Amicus.

Beth Thurberg is an employee of Sanofi Genzyme.

The other authors declare that they have no competing interests in relation to this work.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation of Laboratorio de Neuroquímica Dr. N. Chamoles, Buenos Aires, Argentina.

References

[1] M.T. Muñoz-Yagüe, J.C. Marín, F. Colina, C. Ibarrola, G. López-Alonso, M.A. Martín, J.A. Solís-Herruzo, Chronic primary intestinal pseudo-obstruction from visceral myopathy, Rev. Esp. Enferm. Dig. 98 (4) (2006) 292–302.
[2] V. Stanghellini, M. Camilleri, J.R. Malagelada, Chronic idiopathic intestinal pseudo-obstruction: clinical and intestinal manometric findings, Gut 28 (1987) 5–12.
[3] C. Di Lorenzo, Pseudo-obstruction: current approaches, Gastroenterology 116 (1999) 980–987.
[4] J. Politei, B.L. Thurberg, E. Wallace, D. Warnock, G. Serebrinsky, C. Durand, A.B. Schenone, Gastrointestinal involvement in Fabry disease. So important, yet often neglected, Clin. Genet. 89 (1) (2016) 5–9.
[5] A. Tuttolomondo, Anderson Fabry disease: a multiorgan metabolic disease susceptible of treatment, Curr. Pharm. Des. 19 (33) (2013) 5972–5973.
[6] A. Tuttolomondo, R. Pecoraro, I. Simonetta, S. Miceli, V. Arnao, G. Licata, A. Pinto, Neurological complications of Anderson-Fabry disease, Curr. Pharm. Des. 19 (33) (2013) 6014–6030.
[7] C.R. Scott, S. Elliott, N. Buroker, L.I. Thomas, J. Keutzer, M. Glass, M.H. Gelb, F. Turecek, Identification of infants at risk for developing Fabry, Pompe, or mucopolysaccharidosis-I from newborn blood spots by tandem mass spectrometry, J. Pediatr. 163 (2) (2013) 498–503.
[8] R. De Giorgio, G. Sarnelli, R. Corinaldesi, V. Stanghellini, Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction, Gut 53 (2004) 1549–1552.
[9] C.M. Eng, J. Fletcher, W.R. Wilcox, et al., Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry registry, J. Inherit. Metab. Dis. 30 (2) (2007) 184–192.
[10] B. Hoffmann, M. Schwarz, A. Mehta, S. Keshav, Fabry outcome survey European investigators. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy, Clin. Gastroenterol. Hepatol. 5 (12) (2007) 1447–1453.
[11] P. Buda, J. Ksiazyk, A. Tylki-Szymanska, Gastroenterological complications of Anderson-Fabry disease, Curr. Pharm. Des. 19 (33) (2013) 6009–6013.
[12] D.A. Laney, D.S. Peck, A.M. Atherton, L.P. Manwaring, K.M. Christensen, S.P. Shankar, D.K. Grange, W.R. Wilcox, R.J. Hopkin, Fabry disease in infancy and early childhood: a systematic literature review, Genet. Med. 17 (5) (2015) 323–330.
[13] M. Ries, U. Ramaswami, R. Parini, B. Lindblad, C. Whybra, I. Willers, A. Gal, M. Beck, The early clinical phenotype of Fabry disease: a study on 35 European children and adolescents, Eur. J. Pediatr. 162 (11) (2003) 767–772.
[14] B. Hoffmann, M. Schwarz, A. Mehta, S. Keshav, Fabry outcome survey European investigators. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy, Clin. Gastroenterol. Hepatol. 5 (12) (2007) 1447–1453.
[15] L.S. Friedman, S.E. Kirkham, J.R. Thistlethwaite, D. Platika, E.H. Kolodny, M.D. Schuffler, Jejunal diverticulosis with perforation as a complication of Fabry's disease, Gastroenterology 86 (3) (1984) 558–563.
[16] D.L. Jardine, M.A. Fitzpatrick, W.D. Troughton, A.B. Tie, Small bowel ischaemia in Fabry's disease, J. Gastroenterol. Hepatol. 9 (2) (1994) 201–204.
[17] C.I. Jack, A.I. Morris, D.G. Nasmyth, N. Carroll, Colonic involvement in Fabry's disease, Postgrad. Med. J. 67 (788) (1991) 584–585.
[18] A.P. Burlina, K.B. Sims, J.M. Politei, G.J. Bennett, R. Baron, C. Sommer, A.T. Møller, M.J. Hilz, Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel, BMC Neurol. 11 (2011) 61.
[19] E.L. Wallace, H. Fatima, L.J. Jackson, D.G. Warnock, Appendiceal tissue confirmation of Fabry's disease, Kidney Int. 88 (2) (2015) 417.
[20] K. Deniz, A. Yurci, A. Yağbasan, F. Tekelioğlu, S. Gürsoy, K. Güven, Colonic involvement in Fabry disease, Int. J. Surg. Pathol. 19 (6) (2011) 777–778.
[21] J.W. Rowe, J.I. Gilliam, T.A. Warthin, Intestinal manifestations of Fabry's disease, Ann. Intern. Med. 81 (5) (Nov 1974) 628–631.
[22] B.D. O'Brien, et al., Pathophysiologic and ultrastructural basis for intestinal symptoms in Fabry's disease, Gastroenterology 82 (5) (1982) 957–962.
[23] J. Lakomá, R. Rimondini, V. Donadio, R. Liguori, M. Caprini, Pain related channels are differentially expressed in neuronal and non-neuronal cells of glabrous skin of Fabry knockout male mice, PLoS One 9 (10) (2014), e108641. .
[24] J. Lakomá, R. Rimondini, A. Ferrer Montiel, V. Donadio, R. Liguori, M. Caprini, Increased expression of Trpv1 in peripheral terminals mediates thermal nociception in Fabry disease mouse model, Mol. Pain 12 (Aug 16 2016) (pii: 1744806916663729) 10.1177/1744806916663729.
[25] S.M. Brierley, P.A. Hughes, A.M. Harrington, G.Y. Rychkov, L.A. Blackshaw, Identifying the ion channels responsible for signaling gastro-intestinal based pain, Pharmaceuticals (Basel) 3 (9) (2010) 2768–2798.
[26] R.J. Hopkin, J.L. Jefferies, D.A. Laney, V.H. Lawson, M. Mauer, M.R. Taylor, W.R. Wilcox, Fabry pediatric expert panel. The management and treatment of children with Fabry disease: a United States-based perspective, Mol. Genet. Metab. 117 (2) (2016) 104–113.
[27] F. Dehout, D. Roland, S. Treille de Granseigne, B. Guillaume, L. Van Maldergem, Relief of gastrointestinal symptoms under enzyme replacement therapy in patients with Fabry disease, J. Inherit. Metab. Dis. 27 (4) (2004) 499–505.
[28] J.E. Wraith, A. Tylki-Szymanska, N. Guffon, et al., Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease, J Pediatr 152 (4) (2008) 563–570.
[29] L. Borgwardt, U. Feldt-Rasmussen, A.K. Rasmussen, M. Ballegaard, A. Meldgaard Lund, Fabry disease in children: agalsidase-beta enzyme replacement therapy, Clin. Genet. 83 (5) (2013) 432–438.
[30] C.M. Eng, N. Guffon, W.R. Wilcox, D.P. Germain, P. Lee, S. Waldek, et al., Safety and efficacy of recombinant human alpha-galactosidase A-replacement therapy in Fabry's disease, N. Engl. J. Med. 345 (1) (2001) 9–16.
[31] R. Schiffmann, J.B. Kopp, H.A. Austin 3rd, S. Sabnis, D.F. Moore, T. Weibel, et al., Enzyme replacement therapy in Fabry disease: a randomized controlled trial, JAMA 285 (21) (2001) 2743–2749.
[32] R.J. Desnick, Enzyme replacement therapy for Fabry disease: lessons from two alpha-galactosidase A orphan products and one FDA approval, Expert. Opin. Biol. Ther. 4 (7) (2004) 1167–1176.
[33] C. Tøndel, L. Bostad, K.K. Larsen, A. Hirth, B.E. Vikse, G. Houge, E. Svarstad, Agalsidase benefits renal histology in young patients with Fabry disease, J. Am. Soc. Nephrol. 24 (1) (2013) 137–148.
[34] R. Skrunes, E. Svarstad, K. Kampevold Larsen, S. Leh, C. Tøndel, Reaccumulation of globotriaosylceramide in podocytes after agalsidase dose reduction in young Fabry patients, Nephrol. Dial. Transplant. (May 17 2016) (pii: gfw094).
[35] F. Weidemann, J. Krämer, T. Duning, M. Lenders, S. Canaan-Kühl, A. Krebs, H. Guerrero González, C. Sommer, N. Üçeyler, M. Niemann, S. Störk, M. Schelleckes, S. Reiermann, J. Stypmann, S.M. Brand, C. Wanner, E. Brand, Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch, J. Am. Soc. Nephrol. 25 (4) (2014) 837–849.