ORIGINAL ARTICLE

Cystinosis: a truly orphan disease. Report of the Cystinosis Foundation India

Rajan Ravichandran
Chairman, Cystinosis Foundation India; Director, MIOT Institute of Nephrology, MIOT Hospitals, Chennai, India

Open access

Correspondence to
Rajan Ravichandran
Cystinosis Foundation India
95/42, GF1, RAMS Flat
2nd Main Road, Gandhi Nagar
Adyar - Chennai 600 020
Tamilnadu, India
Tel +91 44 64560090
Email ravidoc55@yahoo.co.in

Author contribution
Acquisition of data, preparation of manuscript, final approval

Competing interest
None declared

Funding information
Cystinosis Foundation India

Received: 13 August 2015
Accepted: 9 April 9 2016

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n. 305690 RARE-Bestpractices project www.rarebestpractices.eu.
Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

Abstract

Cystinosis is a rare disease leading to accumulation of cystine in lysosomes causing apoptotic cell death leading to organ dysfunction. Although the disease was identified 100 years ago, the history of cystinosis in India is really pathetic. Only in 2012, the Cystinosis Foundation India was formed with the initiative to pool up these unfortunate patients. Nineteen patients have been identified and registered with the foundation. Out of these, only 8 are receiving specific therapy with cysteamine. Four patients have undergone successful kidney transplantation. Eight patients have died since registering with the foundation. Seventeen patients were picked up with advanced growth retardation and renal failure. Only 2 children were picked up in early stage. This article describes the difficulties faced in the identification and management of these patients in India.

Key words

Cystinosis, renal failure, growth retardation, cysteamine, India.

Introduction

Cystinosis is an autosomal recessive disorder caused by mutation of the CTNS gene on chromosome 17 which encodes a ubiquitous cystine specific transporter in the lysosomal membrane [1]. There is massive intra lysosomal accumulation of cystine due to the transport defect leading to apoptotic cell death and progressive organ dysfunction. The disease manifests itself around 6 months of life with failure to grow. Signs of Fanconi's syndrome (polyuria, polydipsia, dehydration and acidosis) also appear as early as 6 months. Corneal crystals diagnostic of cystinosis can be present before 1 year, but is always present after the age of 16 months [2]. Untreated, the children progressively develop rickets, severe growth retardation, renal failure and die between 10-15 years of age. The treatment of the disease essentially is to identify early in the first year of life, replace the nutrients and specific treatment with cysteamine. The diagnosis is confirmed by estimating the leukocyte cystine level and identify the genetic mutation. In 1976, Crawhall reported the news of cysteamine resulting in efflux of cystine from the lysosomes [3]. Gahl showed that protracted oral therapy with cysteamine depleted the organ cystine and delayed the complication of cystinosis [4].

So far there have been hardly any reports of cystinosis from India. Phadke et al reported in 2004 a 3 year-old child who presented with Fanconi syndrome with mild renal failure and corneal crystals [5]. The child was initiated on treatment and lost follow-up. In 2014, Krishnan Swaminathan reported the agony of a boy whose diagnosis of cystinosis got delayed in spite of visiting several hospitals ultimately presenting with severe renal failure and growth retardation [6]. The sister of that patient had also died at the age of 7 of a similar condition. In 2015, Sharma reported the biopsy finding in a 3 year-old child with cystinosis and renal failure [7]. Akhilesh Kumar and Bachhawat have discussed the molecular basis of cystinosis [8]. Taosheng Huang reported the details of CTNS mutation in an Indian boy with nephropathic cystinosis [9].

The first successful kidney transplantation in a severely growth retarded child with cystinosis was reported from Chennai, India in 2010 [10]. Subsequently, when the

child attended the school, he was not able to see the black board and the eye examination confirmed the presence of crystals in the cornea. The diagnosis of cystinosis was made retrospectively and his 2 year-old brother was identified with the disease on further investigation. It was this episode that lead to the formation of Cystinosis Foundation of India in 2012. The foundation was launched on May 2012 in Chennai by a NGO Sapiens Health Foundation. Important members of the society from different professions like law, accountancy, journalism etc were made advisors of the foundation. Donations were raised from the general public to run the foundation.

Materials and methods

After the foundation was launched in Chennai, several nephrologists and ophthalmologists in leading centers throughout India were contacted to register their patients with cystinosis. Booklets were distributed in leading nephrology conferences held in the last 3 years. Once the patient was registered, the clinical details including the biochemical workup were included in the records of the registry. Approximately 1100 nephrologists were contacted throughout the country by email correspondence. This paper highlights the clinical data of these patients, the lack of treatment for cystinosis throughout the country as a whole and the difficulties faced in procuring the drug for these patients.

Results and discussion

The effort of the foundation bore fruit and 19 patients have been registered so far in the foundation. Out of the 19 children registered, 4 are females and rest males (Table 1). Only 4 children could be picked up below the age of two. All the children had growth retardation and Fanconi syndrome (Figure 1). Only in 2 children, the creatinine clearance was normal. Seventeen of them had renal impairment including 4 patients having undergone kidney transplantation. One patient continues to be on peritoneal dialysis after failed graft 12 years ago. She is the eldest with the age of 20 years. 8 patients have already died after registering in the foundation. Only 8 patients are continuing on specific treatment with cysteamine although 13 were initiated. None of the patients are using the cysteamine eye drops. Consanguinity in the parents was noted in

Table 1. Details of the patients registered with the foundation and follow-up

No.	Date of registration	Age at the time of registration	Sex	Clinical manifestations*	Affected sibling	Corneal crystal	Hypothyroidism	Cysteamine treatment	Follow-up	Consanguinity in parents
1	01/03/12	12	M	GR, FS, RF, RTX	Yes	Yes	Yes	Yes	Yes	Yes
2	01/03/12	07	M	GR, FS, RF	Yes	Yes	Yes	Yes	Yes	Yes
3	May 2012	10	M	GR, FS, RF	No	Yes	Yes	No	Died	No
4	01/03/12	10	M	GR, FS, RF, RTX	No	Yes	No	No	No	No
5	01/03/12	11	M	GR, FS, RF, RTX	No	Yes	No	Yes	Yes	Yes
6	15/10/12	10	M	GR, FS, RF	No	Yes	No	Yes	Yes	No
7	06/08/12	06	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
8	20/08/12	07	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
9	29/08/12	08	F	GR, FS, RF	Yes	Yes	Yes	No	Died	Yes
10	06/10/12	01	M	GR, FS	Yes	Yes	Yes	Yes	Yes	Yes
11	06/10/12	10	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
12	27/01/13	02	M	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
13	27/01/13	04	F	GR, FS, RF	Yes	Yes	Yes	Yes	Died	Yes
14	16/08/13	12	M	GR, FS, RF	Yes	Yes	Yes	Yes	Yes	No
15	02/04/14	20	F	GR, FS, RF, RTX in 2002, failed graft, CAPD	No	Yes	No	No	Yes	No
16	18/04/14	02	M	GR, FS, RF	No	Yes	Yes	No	Died	Yes
17	03/10/14	03	M	GR, FS, RF	No	Yes	No	Yes	Yes	No
18	20/11/14	05	M	GR, FS, RF	No	Yes	Yes	No	Yes	No
19	03/01/15	02	F	GR, FS	No	Yes	No	Yes	Yes	No

*GR: growth retardation; RF: renal failure; FS: Fanconi's syndrome; RTX: renal transplantation.

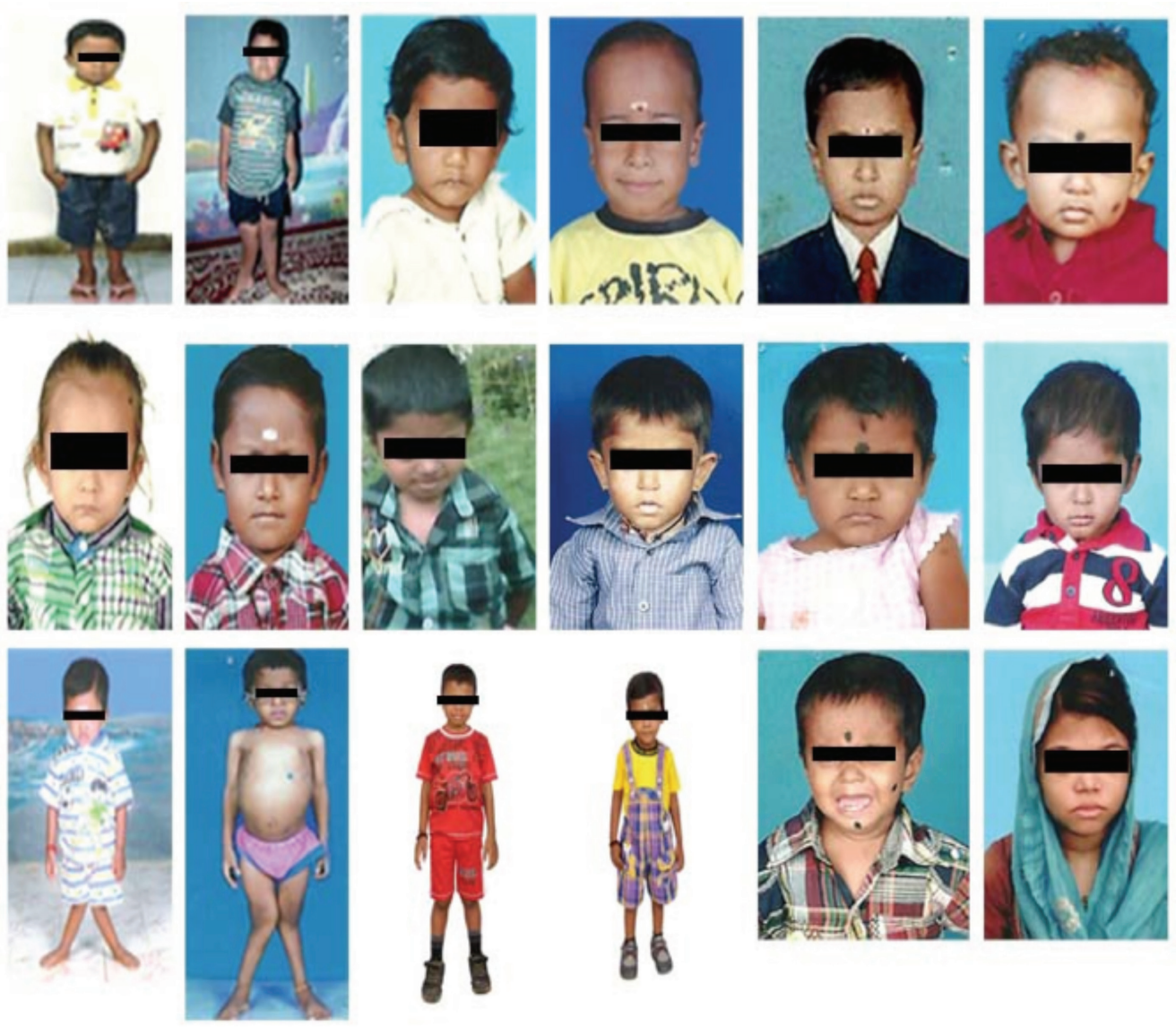

Figure 1. Photographs of the 18 children registered with the foundation.

11. Thirteen patients had hypothyroidism. Corneal crystals were found in all the patients. Three of the children had an affected sibling. Three other children gave a history of similar illness in the sibling who had died earlier. In 2 of the children, the disease was picked up early in life because of the correct diagnosis in the affected sibling.

The treating physicians were contacted, giving more information about the disease and the need for specific treatment. The test, cystine estimation in leukocyte, is not available in India. Hence samples have to be sent to USA for confirmation. Next came the biggest challenge procuring cysteamine for the patients. Cysteamine is not approved for use in India. Hence Orphan Europe could not sell the product in India. The individual patients have to apply to the drug controller for a special permission to import the drug. After that, money had to be remitted to Orphan Europe by individual patients. The cost of the drug is phenomenally expensive with none of the patients getting reimbursement from insurance. Approximately 200 euros is required for a treatment period of 3 months per child. The drug which is then sent by courier requires to be cleared from customs which again involves a 5 to 20% duty. Out of the 19 patients, only 13 were able to procure the drug. Five patients on the drug have died. At present 8 patients are continuing the drug. The Foundation raises the money by donation and is sponsoring the drug for these patients. Attempt has been made to manufacture the drug locally. The eye drops which are required to improve the corneal deposit are not available. The government does not permit the drops to be formulated by

the pharmacy. Big pharma companies are not interested in manufacturing the eye drops because of the low number of patients. It is almost impossible to import the eye drops since it is much more expensive than the oral drug. Attempts have been made to contact Orphan Europe, Raptor Pharma & Sigma Tau Pharma to apply for approval of the oral drug and eye drops in India.

This situation can be dramatically improved if pediatricians pick up the disease in the first year of life itself, so that treatment can be instituted before the child develops complications. This is possible if the test for cystinosis is made available at least in the major cities of India. The drug cysteamine should also be indigenously manufactured, bringing down the cost resulting in adequate therapy to all patients. The Indian Institute of Technology (IIT, Madras), a quasi government organization, has already produced the drug cysteamine in the laboratory and one of the pharmaceutical companies has agreed to manufacture commercially.

Conclusion

Thus, cystinosis has been a totally neglected disease in India with very poor awareness amongst the medical fraternity to pick up the disease early. Procuring cysteamine has been very expensive and difficult. The only light seen is the formation of the Cystinosis Foundation, India in 2012 with subsequent attempts in the right direction.

Acknowledgements

The author wants to thank Kannan S, Research Coordinator, Madras Institute of Nephrology Research Pvt. Ltd, Chennai, India.

References

1. Anikster Y, Shotelersuk V, Gahl W A. CTNS mutations in patients with cystinosis. Hum Mutat 1999;14:454-8.
2. Nesterova G, Gahl WA. Cystinosis. 2001 Mar 22 (updated 2014, Jan 30). In: Pagon RA, Adam MP, Ardinger HH, et al (eds). GeneReviews® (Internet). Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1400/
3. Thoene JG, Oshima RG, Crawhall JC. Intracellular cystine depletion by aminothiols in vitro and in vivo. J Clin Invest 1976; 58(1):180-9.
4. Gahl W A, Charnas L, Markello TC, Bernardini I, Ishak KG, Dalakas MC. Parenchymal organ cystine depletion with long-term cysteamine therapy. Biochem Med Metab Biol 1992;48(3):275-85.
5. Phadke KD, Kumar PA, Karthik S, Bagirath A. Infantile nephropathic cystinosis. Indian J Nephrol 2004;14:18-21.
6. Swaminathan K, Jeyaraman M. Cystinosis: an eye opener. Apollo Medicine 2014;11(1):43-5.
7. Sharma A, Gupta R, Senthil SK, Bagga A, Dinda AK. Giant cell transformation of podocytes: a unique histological feature associated with cystinosis. Indian J Nephrol 2011;21:123-5.
8. Kumar A, Bachhawat AK. A futile cycle, formed between two ATP-dependant y-glutamyl cycle enzymes, y-glutamyl cysteine synthetase and 5-oxoprolinase: the cause of cellular ATP depletion in nephritic cystinosis. J Biosci 2010;35(1):21-5.
9. Tang S, Danda S, Zolcikhacian M, Simon M, Huang T. An Indian boy with nephropathic cystinosis: a case report and molecular analysis of CTNS mutation. Genet Test Mol Biomarkers 2009;13(4):435-8.
10. www.cystinosisindia.org