International Journal of Contemporary Pediatrics
Bajaj S et al. Int J Contemp Pediatr. 2022 Sep;9(9):851-854
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20222126

Case Report

Telegenetics aids the diagnosis of Hunter syndrome caused due to a novel IDS variant in rural India, during COVID-19 pandemic

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Received: 28 June 2022
Revised: 30 July 2022
Accepted: 03 August 2022

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ABSTRACT

The COVID-19 pandemic resulted in an expanded application of telemedicine globally. This enhanced connectivity also opened newer arenas of availability of super-specialty consultations in remote India. The current report highlights the details of a 15-month-old boy from a rural Maharashtra who was diagnosed with Hunter syndrome (HS i.e., mucopolysaccharidosis (MPS-II) via hybrid model of consultation involving telemedicine. The child was first evaluated by a paediatrician in-person, when he was suspected to have one of the MPS subtypes. This was followed by a virtual and an in-person consultation with the clinical geneticist, following which the suspicion for MPS was sharpened further. Exome sequencing identified a novel insertion in IDS gene c.1080_1081insGAATAA, p.Ile360_Phe361insGluTer confirming HS. The mother was identified to be a carrier for this X-linked disorder. The family was counselled about their available reproductive options for the future. The option of enzyme replacement therapy, as a potential lease of life, for improvement of the somatic symptoms, quality and longevity of life, was offered. However, due to the exorbitant lifelong expense that ERT entailed and the lifelong, weekly-injection schedule; the family declined this option. The report highlights the diagnostic journey of a child with HS, which spanned over barely two months following presentation to the specialist. It demonstrates how prudent integration of telemedicine services in resource-limited and pandemic-challenged settings, can help truncate the diagnostic odysseys often borne by patients of rare diseases. It also calls for attention to fill the existing gaps in meaningful healthcare directed towards rare diseases.

Keywords: Telemedicine, Genetic counselling, Enzyme replacement therapy, Exome sequencing, Mucopoly-saccharidosis, Rare diseases

INTRODUCTION

Several studies have been published globally about the impact of the pandemic on genetic services.[1-5] A review on telegenetic services showed high acceptability for it in underserved communities, with reduced travel and cost-effectivity being major advantages. With a critical shortage of genetic experts in the country, combined with a mammoth population of 1.3 billion, over half of whom live in rural areas, there is very little scope for access to genetic services. Clinicians catering to remote and underserved populations have previously cited lack of time and a dearth of genetic experts as primary hindrances for integration of genetic services.[6] There are merely 75 qualified geneticists and less than 250 certified genetic counsellors in the country, highlighting a dearth

of qualified experts.[7,8] Moreover, genetic testing without appropriate consultation has shown to result in over-testing, increased costs and lesser yield.[9] Telegenetics thus has a potential to bridge the gap by giving access to individuals in tier II and III cities to genetic services. Furuya et al recently described a 'hybrid model' of healthcare that relies on a blend of teleconsultations and in-person consultations.[10]

CASE REPORT

We report a case of mucopolysaccharidosis-II with a novel IDS variant. Notably, the child was offered a confirmed diagnosis within two months of the first visit to the specialist, through a hybrid model of healthcare, in the challenging background of an ongoing COVID-19 pandemic. A 13-month-old male, residing at Karve village (Maharashtra), presented to a paediatrician in Nipani, Karnataka (~68 kilometres away from home), with delayed milestones, history of bilateral inguinal hernia repair, frequent colds, disturbed sleep and excessive snoring. The child had normal growth parameters. After ruling out primary hypothyroidism, the primary physician seeked telegenetic consultation for suspected MPS. The geneticist was based in Mumbai while the patient consulted from the paediatrician's clinic in Nipani (~400 kilometres distance). This teleconsult was unique since the referring paediatrician was present during the telemeeting, thus enabling more meaningful transmission of medical information to the other end. Teleconsult helped the geneticist note relative macrocephaly, adenoid facies, bossed skull, large mouth, depressed nasal bridge, anteverted nares and mild midface hypoplasia (Figure 1). The child also had pallor, pectus carinatum and large mongoloid spots on the back. Reports showed elevated urine glycosaminoglycans (GAGs) by spectrophotometer (10-times normal upper limit). Suspecting MPS-spectrum, the geneticist requested for complete blood count, echocardiogram, skeletal survey, abdomen sonogram, auditory brainstem response, otorhinolaryngology consultation for suspected adenoid hypertrophy and ophthalmic evaluation.

One-month later the child followed up physically/in-person at Kolhapur in a paediatric genetics outpatient service department (OPD) (~77 kms from hometown). The geneticist had travelled from Mumbai to the centre in Kolhapur (~377 kms away) for the 6-weekly outstation genetics OPD. Work-up ordered a month prior indicated adenoid hypertrophy, anaemia, mild hepatomegaly and dysostosis multiplex. Based on the clinical history, an exome sequencing (ES) test was performed for definitive diagnosis. ES revealed a novel insertion of 6-base-pairs in *IDS* gene NM_000202.8 c.1080_1081insGAATAA causing amino-acid insertion (p.Ile360_Phe361-insGluTer). The insertion was predicted to cause loss of normal protein function through protein truncation. The variant has not been reported in population databases, nor been identified in any affected individuals so far. The variant was classified as likely-pathogenic as per the ACMG guidelines (Richards et al, 2015). Parental Sanger analysis confirmed the mother to be a carrier for the identified variant (Figure 1).

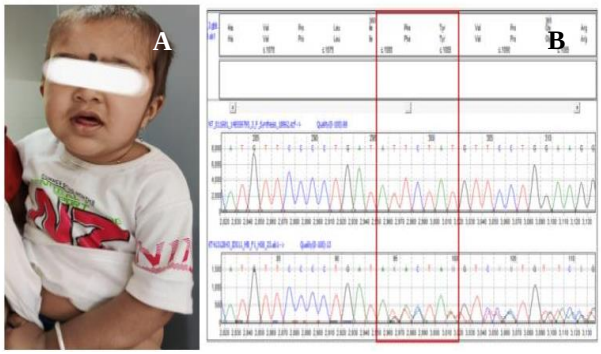

Figure 1: A) Frontal photograph of the child revealing facial dysmorphisms, B) Maternal Sanger sequencing data (electropherogram) showing the provided Mother sample showing nucleotide change at chrX: c.1080_1081insGAATAA, (p.Ile360_Phe361insGluTer) in IDS gene.

This confirmed the diagnosis of MPS-II (Hunter syndrome-HS) in the proband, inherited from his mother. One month later, in May 2021, coinciding with the second wave of COVID19 in India; post-test genetic counselling was offered over a teleconsultation from Mumbai (Figure 2). The X-linked inheritance, chronic progressive nature of MPS-II, potentially multisystemic involvement and early death in the absence of specific therapy, were explained. The need for periodic surveillance was highlighted. Nerve conduction study of the median nerve to rule out carpal tunnel syndrome, polysomnography and MRI brain were requested to be performed once the pandemic settled. They were explained the available reproductive options to avoid a recurrence of the same condition. They were offered enzyme replacement therapy (ERT) as a potentially life-saving drug for MPS-II. Its advantages, limitations and the cost challenges were outlined. The family, however, declined ERT for the child.

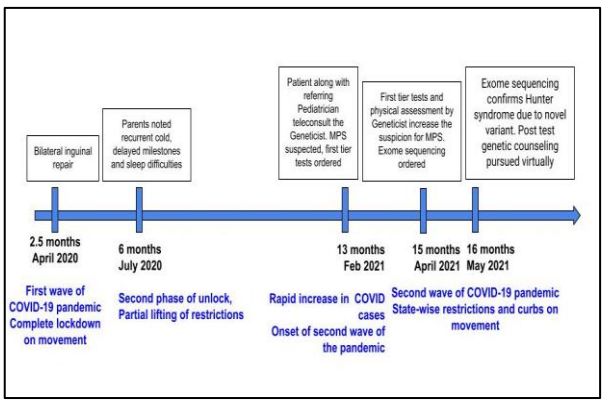

Figure 2: Timeline to the patient's diagnostic journey.

DISCUSSION

Rare diseases (RD) are often life-limiting and multisystemic.[11] An accurate diagnosis is vital for correct management, medical and psychological support and family planning.[12] However, the average time taken for an individual affected with RD to reach the correct diagnosis can be as delayed as six years.[13] In our case, the tele-platform helped initiate a targeted work-up in a travel-restricted environment. Given that the background investigations were available during the physical meeting and follow-up, the subsequent suspicion for lysosomal storage disorder (LSD), specifically MPS, was more straightforward and a genomic diagnosis of MPS-II was reached within two months from expert consultation.

While ERT for MPS-II has shown to considerably improve the disease progression and survival rate, it comes with drawbacks. The enzyme is unable to cross the blood-brain barrier and thus can only offer a partial relief to patients with neurological symptoms. It has also been seen to have limited effect on skeletal, heart and corneal symptoms.[14] The approximate annual cost for one of the ERT options for MPS-II in India is 1 crore INR for a 10-kilogram child.[15] This combined with the additional hospitalisation costs and support required from multiple specialists for symptomatic treatment, drives the cost of management to exorbitant levels.[15]

The weekly-infusions of ERT for MPS-II, translate to frequent hospital-visits, often travelling long distances, and taking regular day-offs from work, which can be particularly challenging for daily wagers and low-income strata parents. A National Policy for Rare Diseases (NPRD) was introduced in 2021 by the Government of India that categorised MPS-II under group-3, which includes conditions that require lifelong and expensive treatments.[16] There is no mention of financial support for diseases under this category, leaving patients at the mercy of crowdfunding and voluntary donations. Thus, like in our report, parents often voluntarily, although painfully, opt out of ERT, despite its promising potential. We note the large unmet need for ERT for treatable LSDs in India and the practical challenges towards its realisation.[15] Primary prevention by prenatal diagnosis, appears to be the most effective measure in a resource-limited country like India, to bring down disease burden.

CONCLUSION

We report the journey of a child with HS diagnosed with the aid of telegenetics during the COVID19 pandemic. The case is an example of how prudent integration of telemedicine services in resource-limited settings, can help truncate the diagnostic odysseys borne by patients of RD. Importantly, the report also brings to light the gaping holes in the existing RD policy of the country; specifically with regards to ongoing, lifelong, expensive medicines like ERT.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Bajaj S, Thawani S, Iyer G, Setty PN, Kore M, Jadhav V. Telegenetics aids the diagnosis of Hunter syndrome caused due to a novel IDS variant in rural India, during COVID-19 pandemic. Int J Contemp Pediatr 2022;9:851-4.