The Burden of Diagnosis

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I asked the resident to find out if Baby of Malini (name changed) had undergone the bone marrow transplantation. When the resident doctor called the father of the baby, we got the sad news that bone marrow transplant was not done and the baby had died the previous day. This distressing news brought back the memories of the diagnostic journey which the family had travelled with us, the medical geneticists, or rather we had travelled with the family. The story started more than a year ago. The couple, Malini and her husband, had been referred for prenatal counseling and testing in view of history of death of their two previous offspring due to an undiagnosed illness: one child had died during the neonatal period and the other had died at 6 months. Malini was now 3 months pregnant. There were no medical records available of the affected children and the couple mentioned that the babies had not been thoroughly investigated. There was no consanguinity. The possibility of genetic metabolic disorders was considered and the family was told that in the absence of a definite diagnosis, prenatal diagnosis cannot be provided just on the basis of the suspicion of a genetic disorder. They were told to get newborn screening for inborn errors of metabolism through tandem mass spectrometry (TMS) done for this baby on the 4th day after birth. The couple came back to us after the delivery and TMS was done for the baby (male neonate, yet unnamed, and hence, referred to as Baby of Malini). The report showed a high level of glycine. The CSF glycine level was done, which supported the diagnosis of non-ketotic hyperglycinemia (NKH). The baby was around 3 months old by this time and was asymptomatic. We explained the implications and prognosis of NKH and explained the need for further molecular genetic testing to confirm this diagnosis. NGS (next generation sequencing)-based panel for genetic disorders of infantile onset was ordered as it covers all three genes for non-ketotic hyperglycinemia. To our surprise, the result showed a hemizygous mutation in the *IL2RG* gene, suggesting the diagnosis of severe combined immunodeficiency. This is a known, previously reported mutation and the data showed very good coverage of this gene region indicating that this was a reliable report and this was very likely to be the disease-causing mutation in this family. The mutation was confirmed by Sanger sequencing in the infant as well as his mother, who was a carrier of the same mutation. The family now had to be counselled about this new development in the diagnosis and about the fact that the actual diagnosis was not NKH. It was difficult and confusing for the family to be now assigned a new diagnosis, but with appropriate and detailed counseling they were able to understand. Of course, the high glycine levels remain unexplained.

All these events are described in a few lines here but involved multiple travels for the family from their home to our hospital – a distance of 800km, high costs of the tests, multiple discussions on investigations, their possible results, uncertainties and the diagnostic plans ahead. The puzzle of the previous two infant deaths was solved, but the outcome for this child was poor. The solution came in the form of a problem. In the visit when the mutation reports became available and were discussed, the baby was noted to have tachypnoea. Investigations revealed that he had severe pneumonia - this was the first significant episode of infection in this immunodeficient infant. After having been explained the need for intensive care treatment for the present episode of severe pneumonia, the parents decided to get the child hospitalized in their hometown. A few weeks later, we got a call from the parents that the baby was discharged and was better. The option of bone marrow transplant was explained to them and

our last communication with the family was when they were travelling with the baby to New Delhi for pursuing this option- we gave them information about the pediatric haematologist and bone marrow transplant specialist in Delhi. We were hoping that the dramatic diagnosis achieved after the long, costly and cumbersome investigational journey would lead to an equally dramatic cure and happiness for the family, but sadly it did not happen.

Though each genetic disorder is given a single OMIM number, in reality, each case and each family affected even with the same genetic disorder is different. The diagnostic challenges faced by the clinician and the counselling issues are huge. But far more enormous are the agony, the anguish, the anxiety created by the large number of investigations, and the financial and psychological burden on the families, while travelling through this journey full of uncertain stops and uncertain destinations. Many times, one may not reach the destination of cure or may not be able to fulfil the prospect of having an unaffected child. Next generation sequencing has made diagnosis possible in situations where, until a few years ago, there seemed to be no hope of identifying the cause. But the flip side of these genomic techniques are the uncertainties about the pathogenicity of the novel variations detected, which make understanding of the implications even more difficult for laypersons. Continued communications about the tests ordered, possible results and their implications and counselling helps greatly in getting the desired cooperation of the patient and families and lessens the anxieties associated with the diagnostic odyssey. The treating physicians and geneticists need to take the patient and family along and respect their autonomy as well. The educational and economic status of the patients and their families does not necessarily determine their ability to understand the test results, interpret them correctly and take appropriate decisions. Many such families teach the doctor coping strategies, humane values and strength of character. Stability in adversity is indeed the most important virtue to sail the seas of life and for doctors and families dealing with genetic disorders, to sail through the unchartered expanse of the genome!