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Review Article

Genetic counselling for inborn error of metabolism

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ABSTRACT

Inborn error of metabolic (IEM) disorders being an important contributor for neonatal morbidity and mortality require unique and multidisciplinary health care including genetic counselling to reduce the burden of these disorders and to improve the quality of life of the patient. Genetic counselling, besides its basic elements, clinical genetic aspects and management of IEMs; also helps to understand family's knowledge and attitude towards the disorder, to motivate them to accept and adapt to the situation. Through this paper we are sharing our experience of providing genetic counselling to patients of metabolic disorders and emphasizing the role of counselling in imparting right directive care and to find possible ways to face the formidable challenges.

Keywords: Inborn error of metabolic, Genetic counselling, Pretest, Post test

INTRODUCTION

Counselling a communication process with the major principle of patient autonomy constitutes of various basic elements that individually are very different. It has been practiced from the time of Worldwar II to solve the various social issues of people. During its evolutionary journey the major paradigm shift of counselling from social to medical and then to genetic counseling made the practice of genetic counseling highly peculiar in its features and its values in providing multidisciplinary health care services, resources, supportive care, education by expert counsellors and referrals to patients and their families who suffer from various genetic disorders, it also helps in imparting right directive care and to find possible ways to face the formidable challenges.[1]

Among the various genetic disorders, IEMs resulting from an enzyme defect constitute a huge group of rare genetic disorder with individual incidence of less than 1 per 100,000 births, and collectively incidence may be 1 in 800 to 1in 2500 births.[2] IEMs include diverse group of small and large molecules metabolic defects. The common small molecules defects are carbohydrates, fatty acids, protein disorders, organic acid and mitochondrial disorders and common large molecule defects include lysosomal, paroxysmal defects and others. Small IEMs present with nonspecific and complex spectrum of symptoms such as vomiting, hypoglycemia, metabolic acidosis, lethargy, seizures, encephalopathy and multiple organ failure.

Most of these symptoms depend upon the severity and type of enzyme involvement and are due to either toxic accumulations of substrates or intermediates before the block, or reduced energy production or deficiency of useful products beyond the block, or a combination of all these mechanisms. Some of these disorders can be treated by early diagnosis and early intervention. If these are not treated at time, these may cause irreversible multiple system damage and even early death. But the primary physicians due to the complexity, criticality of these disorders and lack of their expertise, generally hesitate to treat and counsel the parents of the patients, resulting in

increase in burden due to morbidity and mortality due to IEMs. Hence, it should be kept in mind that genetic counselling is an extremely valuable resources for the care and education of patients with IEMs and their family members at the time of the initial diagnosis and later on.[2,3]

The goal of the genetic counselling is not only to provide information about its fundamental elements of counselling but also to make aware the family about the clinical aspects of genetics of IEMs and clinical course and management of the disease; along with it the efforts to understand family's knowledge, acceptance and attitude towards the disorder, to motivate them to adapt to the situation should also be made by a person who is expert both in clinical and counselling aspects. To achieve this we do genetic counselling including different aspects like pretest that is before making the definitive diagnosis, post-test counselling at the time of disclosure of definitive diagnosis, counselling regarding prognosis, management, recurrence risk, preconception and prenatal management counselling, psychosocial counselling at the same time, counselling during follow up visit after establishing the diagnosis and counselling of affected teenage child. It provides families enough time to clear their doubts and to make good rapport with the counsellor. We always prefer family-oriented counselling and it is done in- person but telehealth a convenient and cost-effective facility can also be offered to the families on follow up visit when the presence of the patient is not needed.[4]

During pretest counselling, after getting history, pedigree drawing and detail examination of the patient, we discuss the following aspects with family

Importance of getting definitive diagnosis which in turn can be helpful in management, recurrence risk prediction and prenatal diagnosis. All the details of genetic and miscellaneous tests, various factors affecting the interpretation of the tests, the advantages, limitations and the cost of the tests. All the available auxiliary and confirmatory tests like neuroimaging, magnetic resonance spectroscopy (MRS) and nuclear magnetic resonance (NMR), skeletal survey, basic new born screening tests (NBS), expanded NBS tests tandem mass spectrometry (TMS) (number of screened conditions varies state by state), gas chromatography mass spectrometry (GC-MS), enzyme analysis and new generation sequencing (NGS) based molecular tests' (the diagnostic yield of next generation sequencing reached 64.3%, whole exome sequencing diagnostic yield for complex cases, like mitochondrial disorders, reached 49%) options are also informed.[5]

Counsellor helps the family in facilitating decision making. They are also assured that along with above mentioned tests, the contribution of many free online databases like Online Mendelian Inheritance in man (https://omim.org/), Clinvar (https://www.ncbi.nlm.nih.gov/clinvar/), guidelines on step wise genetic evaluation of IEM by American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG) has made the diagnosis of IEMs easy.[6,7]

Post-test counselling; the time of revealing the definitive diagnosis our discussion includes following facets

Awareness of what does the genetic testing result and condition diagnosed mean. Knowledge about the associated comorbities, prognosis, necessary and complex management of acute crisis. Importance of starting treatment before significant neurological damage occurs. Value of dealing with all the associated comorbities along with primary symptoms. Necessity of special, précised and holistic medical support by a multidisciplinary team which includes pediatrician, metabolic specialist, pediatric dietician to incorporate a medical formula and/or medical foods, social workers, clinical pharmacists, nurses, genetic counselors, neurodevelopment specialists, physio-therapist and rehabilitation experts. Provision of option of centers with facilities of all these services under one roof which can bring the favorable outcome.

Discussion with the family in brief regarding the long-term longitudinal management like maintenance of dietary modification, enzyme replacement therapy (ERT), hematopoietic stem cell therapy, depending upon the need; follow-up visits and the promise of gene therapy in the future in defeating these diseases. Though the cost and availability of these treatment options is a big challenge, still information regarding the above-mentioned modalities is given. They are also informed about the country's regulatory authority- FSSAI for specific diet, charitable organizations, clinical trials and central and state government initiatives for ERT and procedure of procurement of ERT. They are also made aware about various metabolic organizations in India, support networks, advocacy groups, the National Policy for Rare Diseases (NPRD), 2021 (https://main.mohfw) one-time financial support of up to Rs. 50 lakhs in any of the Centre of Excellence (CoE) and Nidan Kendras for the treatment of rare disease patients.

Discussion on carrier status of both the parents and autosomal recessive pattern Inheritance of IEMs and an increased risk (25%) to have an affected child to carriers compared to the general population is done with them. It is not right to hide this information.[8] The consanguineous families are at high risk to be a carrier or to have an affected is also conveyed. Conversation about carrier testing, the prenatal diagnostic options like chorionic villus sampling (CVS) at approximately 11-13 weeks gestation or amniocentesis at approximately 16-20 weeks or the option of preimplantation genetic testing for monogenic disorders (PGT-M) with all the advantages and disadvantages and different reproductive options including the option of mitochondrial transfer also known as three-parent IVF and the risks to other family members is done. Details of the discussion and other important information

is given to the family in writing for primary health care provider's information.

IEM affected child in a family puts different psychosocial effects in a family like cognitive, emotional such as grief, shock, denial, anger, guilt, shame, despair/grief, and sadness, acceptance, social, practical and global, familial, economic and cultural. Each family may suffer from these issues in a different way, so psychosocial counseling based on each one's need is done to make it more effective. Counsellor also keeps in mind the issue of emotional stigma of the family and helps them to adapt to the condition. Dealing with psychosocial issues helps in strengthening a longitudinal relationship between counsellor and patient and his family.[8-10]

During the follow visit generally at 3 months after establishing the diagnosis, we try to put emphasis in providing following information

About the condition again in depth, to clarify misunderstandings of the family, to probe their adapting and managing strategies. We also discuss with the family in- detail regarding the importance of the maintenance of long term longitudinal management modalities and follow-up visits (which depend upon the need of the patient). The discussion regarding various support networks, advocacy groups and the National Policy for Rare Diseases (NPRD) is done again. Along with all these issues, counsellor also tries to understand the attitude of both parents towards condition and towards its management efforts and discuss about it. Discussion regarding it can bring the difference in the attitude of family towards acceptance and management of such patients.[11]

During teenage following are our goals during counselling

Supporting smooth shift of the teenage patient to adult health care unit, helping them in understanding their condition and in taking charge of their care independently to increase the autonomy and compliance to management, informing them about support organizations, social networks and resources for additional assistance. Issues like fertility, pregnancy outcomes, and avoiding an unplanned pregnancy is talked about. Pregnant women patients are encouraged to get counselling so that the specific management interventions can be made.[12]

Though in today's date advancements in the science and technology have improved our knowledge of these IEMs and provision of various diagnostic, therapeutic modalities at an affordable cost and genetic counselling is being made for such patients but still various challenges are being faced in providing counselling and management services up to the mark resulting in unfavorable prognosis for some patients.

The social media, disease specific support groups and online resources are trying to bring a ray of hope of making the genetic counselling a reality in future and changing the prospect of counselling which will help in providing ongoing support, education and minimize the social, mental and emotional sufferings of parents with suspected IEMs.

CONCLUSION

Genetic counselling for metabolic disorders in a stepwise manner can help families with IEMs impart the right directive care and face the social, mental, and emotional challenges.

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