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Short Communication

Newborn screening by liquid chromatography-tandem mass spectrometry: A future perspective in India

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ABSTRACT

Inborn errors of metabolism are genetic disorders in which body cannot properly metabolize food into energy due to the defects in specific enzymes. Newborn screening is performed to rule out the presence of inborn errors of metabolism to prevent serious health problems. In recent years, introduction of mass spectrometry technology worldwide for newborn screening enables rapid and accurate detection of dozens of congenital metabolic disorders. Here, we discuss the perspective of liquid chromatography-mass spectrometry in newborn screening in India.

INTRODUCTION

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is a high grade technique that combines the high resolution analytical separation of high-performance liquid chromatography (HPLC) method with the ultra sensitive mass detection technique of the mass spectrometry (MS) procedure. This technological development has made possible the combined approach of high-sensitivity separation and mass analysis simultaneously for an extensive characterization of conventional as well as specialized clinical chemistry analytes in the crucial areas of therapeutic drug monitoring, detection of inborn errors of metabolism (IEM), estimation of 25-hydroxy Vitamin D, measurement of steroids, hormones and many more with an immense clinical and therapeutic application[1]. Advancement in mass spectrometry together with modern analytical software provides a gold-standard technique with ultra-high-speed detection, significant sample throughput, tremendous sensitivity, high molecular specificity and multiplexing capability. Accurate and consistent results obtained by LC-MS/MS helps in effective diagnosis of various disorders [2].

Newborn screening (NBS) is the screening of babies shortly after birth for a list of congenital disorders that can cause serious problems for the baby if not recognized and treated early. NBS has the potential to identify risk of certain diseases before the appearance of clinical symptoms. Babies with these diseases can appear normal at birth, but irreparable harm such as permanent brain damage, growth retardation, sepsis or death can happen with the onset of clinical symptoms [3]. Early detection of these disorders may save valuable lives as well as high economical burden on the society leading to a healthy future. Here, we discuss about NBS by LC-MS/MS technology and its future perspective in India.

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NBS by LC-MS/MS

LC-MS/MS technology is used to detect levels of several amino acids and acylcarnitines from dried blood spot of babies collected on the specially designed filter paper to rule out the presence of IEM. Various IEM like aminoacidopathies, urea cycle disorders, fatty acid oxidation disorders and organic acidurias are successfully detected by this novel technology.

NBS is ideally performed for babies maximum upto 30 days of age to screen them for IEM and is usually done within 3rd to 5th day of life. However, it may also be done after 24 hours from birth. The test is not recommended before 24 hours of life as some analytes like thyroid-stimulating hormone (TSH) may give false positive results. Moreover, feeding may not be established in babies within this period, which is required to induce metabolism. The screen positive babies are sent for further confirmatory investigations and treatment by metabolic specialists if required. In many cases, restricted and specific diet and/or specific supplementation are sufficient to improve the quality of life, and prevent physical and/or psychological damage.

LC-MS/MS technology provides a new approach to NBS with a capability of screening multiple metabolic disorders by quantifying multiple metabolites in a single analytical run. This unique capacity of LC-MS/MS reduces the turn-around time of the clinical laboratory. Analytical robustness and reproducibility allow for rapid, simultaneous analysis and detection of many disorders of amino acid, organic acid, and fatty acid metabolism from same dried blood sample. Thus, being capable of detecting approximately 50 inborn errors of metabolism in a single test, LC-MS/MS allows a paradigm change from *"one spot, one test, and one disease"* to *"one spot, one test, and many diseases".*

Advantages of LC-MS/MS

Different analytical methods have been deployed to detect abnormal levels of specific metabolites or hormones in the newborn's blood with sufficient reliability and low cost to allow their use as screening methods. However, LC-MS/MS technology has put its tremendous impact in this field in the recent decade because of the following advantages:

1. The technique has high selectivity and specificity.

2. False positive rate is very low, only 0.2-0.33 % of babies is needed to be screened for further testing [4].

3. Sensitivity is close to 100% with high positive predictive value (PPV) [4].

4. Results are highly reproducible.

5. Sample preparation is simple.

6. Sample throughput is very high because of short run time.

7. Rapid screening for multiple metabolic disorders is possible in a single run.

8. Multiple compound classes can be analyzed in a single run.

9. Less of precious sample is required.

10. Wide range of analytes can be analysed.

Limitations of LC-MS/MS

Inspite of the advantages, still there are following challenges facing by clinical laboratories for implementation of this technology in a wider scale:

1. Huge initial investment is needed to set up LC-MS/MS system and related accessories.

2. The technology is little complex to operate, and requires heavy training commitment and skilled personnel.

3. Sample preparation is manual, thus, increasing the possibility of human error.

4. There is lack of online extraction and laboratory information system interfacing for this technology.

5. Inter-instruments standardization, optimization and harmonization are also difficult.

Future perspectives for LC-MS/MS in population-based NBS in India

Implementation of a NBS programme in India is the need of the hour as this country is one of the 5 countries which collectively account for approximately 85% of the total births that happen in Asia Pacific region [5]. As per different reports, incidence of IEM in Indian newborns is quite high [6-8]. NBS has been started quite early in some developed countries. However huge cost of the technology and lack of awareness have made it difficult to implement any population-based NBS programme in India. Recent initiative has been taken by Government of India and pilot projects have been launched in a few states like Goa, Andhra pradesh, Kerala and Chandigarh [9].

From a high-end research platform, mass spectrometry has evolved into a routine analytical tool with a widening landscape in modern times. Today the laboratory specialists have identified and realized the tremendous impact of tandem mass spectrometry especially in the field of NBS. Especially in NBS programme, the footfall of LC-MS/MS has revolutionized the identification of metabolic disorders leading to a pavement of prompt preventive and medical intervention to relieve or treat the disease. Manufactures are coming up with commercially available automated sample preparation modules which indicate the future of total automation in this technology without manual intervention. A few kits are already available in the market to spare the clinical chemists from the laborious tasks of in-house method development and to reduce human errors. Moreover, it will be easier for the clinical laboratories to lower the cost of the tests with increasing sample volume which will be an obvious effect of increasing awareness as well as building-up of public-private partnership. Hence inspite of the huge initial investment and requirement of technical expertise, clinical laboratories are gradually expressing their interests to adopt the LC-MS/MS technology fast. LC-MS/MS in the field of NBS is already a gold-standard technology and new trends indicate its bright future in clinical diagnostic.

Conclusion

Population-based NBS is very essential to build a healthy future generation in India. We genuinely feel that, the day is not so far when population-based NBS by LC-MS/MS technology will get a momentum with the advent and procurement of this technology by clinical laboratories at a large. Government initiative to increase general awareness about NBS will also be very helpful in this respect.

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Contribution

AB: conceptualized and drafted the manuscript. RS: reviewed, edited and formatted the manuscript in the final version.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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