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# Testicular Differential MicroRNA Expression Derived Occupational Risk Factor Assessment in Idiopathic Non-obstructive Azoospermia Cases

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**Abstract :** Purpose: To investigate microRNAs (miRNA) as an epigenomic etiological factor in idiopathic non-obstructive azoospermia (NOA). In order to achieve the same, an association was seen between occupational exposure to radiation, thermal, and chemical factors and idiopathic cases of non-obstructive azoospermia, and later, testicular differential miRNA expression profiling was done in exposure group NOA cases. Method: It is a prospective study in which 200 apparent idiopathic male factor infertility cases, who have been advised to undergo testicular fine needle aspiration (FNA) evaluation, are recruited. A detailed occupational history was taken to understand the possible type of exposure due to the nature and duration of work. A total of 26 patients were excluded upon XY-FISH and Yq microdeletion tests due to the presence of genetic causes of infertility, 6 hypospermatogeneis (HS), six Sertoli cell-only syndrome (SCOS), and six normospermatogeneis patients testicular FNA samples were used for RNA isolation followed by small RNA sequencing and nCounter miRNA expression analysis. Differential miRNA expression profile of HS and SCOS patients was done. A web-based tool, miRNet, was used to predict the interacting compounds or chemicals using the shortlisted miRNAs with high fold change. The major limitation encountered in this study was the insufficient quantity of testicular FNA sample used for total RNA isolation, which resulted in a low yield and RNA integrity number (RIN) value. Therefore, the number of RNA samples admissible for differential miRNA expression analysis was very small in comparison to the total number of patients recruited. Results: Differential expression analysis revealed 69 down-regulated and 40 up-regulated miRNAs in HS and 66 down-regulated and 33 up-regulated miRNAs in SCOS in comparison to normospermatogenesis controls. The miRNA interaction analysis using the miRNet tool showed that the differential expression profiles of HS and SCOS patients were associated with arsenic trioxide, bisphenol-A, calcium sulphate, lithium, and cadmium. These compounds are reproductive toxins and might be responsible for miRNA-mediated epigenetic deregulation leading to NOA. The association between occupational risk factor exposure and the non-exposure group of NOA patients was not statistically significant, with $\chi^2$ (3, N= 178) = 6.70, p= 0.082. The association between individual exposure groups (radiation, thermal, and chemical) and various sub-types of NOA is also not significant, with $\chi^2$ (9, N= 178) = 15.06, p= 0.089. Functional analysis of HS and SCOS patients' miRNA profiles revealed some important miR-family members in terms of male fertility. The miR-181 family plays a role in the differentiation of spermatogonia and spermatocytes, as well as the transcriptional regulation of haploid germ cells. The miR-34 family is expressed in spermatocytes and round spermatids and is involved in the regulation of SSCs differentiation. Conclusion: The reproductive toxins might adopt the miRNA-mediated mechanism of disease development in idiopathic cases of NOA. Chemical compound induced; miRNA-mediated epigenetic deregulation can give a future perspective on the etiopathogenesis of the disease.

**Keywords :** microRNA, non-obstructive azoospermia (NOA), occupational exposure, hypospermatogenesis (HS), Sertoli cell only syndrome (SCOS)
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