

TIMELINESS OF GENETIC DIAGNOSIS IN CRITICAL NEWBORNS: PROPOSAL OF A DEDICATED DIAGNOSTIC PATH

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SUMMARY

We present the encouraging preliminary data of a diagnostic process dedicated to critical infants with suspected genetic disorders admitted to the NICU of the Bambino Gesù Children's Hospital in Rome, Italy, during the period between January and December 2019.

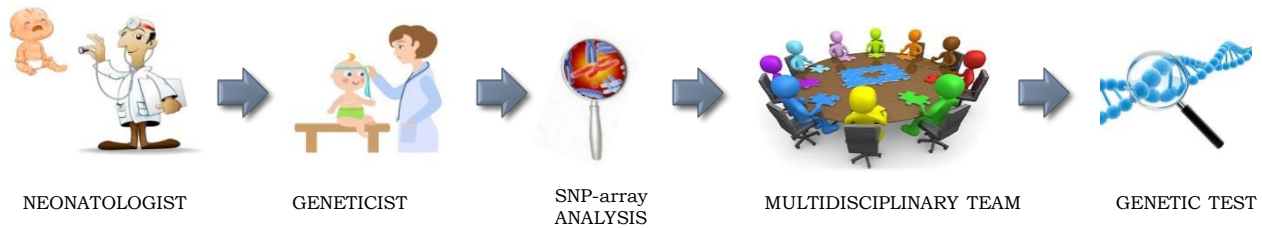
BACKGROUND

Genetic disorders are one of the leading causes of infant morbidity and mortality and are frequent in Neonatal Intensive Care Units (NICUs). However, the exact prevalence of genetic diseases, especially monogenic conditions, among patients admitted to NICUs is not yet known and only in 10-20% of cases an etiological diagnosis is made. In recent years, medical genetics has gained an increasingly important role in clinical practice thanks to the development of new analysis techniques, such as CGH-array and Next Generation Sequencing (NGS). Literature data show that NGS technologies, particularly Whole Exome Sequencing (WES), used in ill infants can have a diagnostic yield in approximately 36.7% to 57% of cases with a change in medical care between 52% and 71.9%.

PARTECIPANTS AND METHODS

A total of 12 patients were enrolled, the mean age was 85 days. All patients were in critical clinical condition. A major congenital anomaly was present in 10/12 infants, 1 patient had chronic diarrhea and 1 suspected cholestatic jaundice. Patients were evaluated by a clinical geneticist and pathogenetic CNVs were excluded by SNP-array analysis. Each clinical case was discussed with a multidisciplinary team to perform the most appropriate genetic test.

The following diagnostic tests were performed: clinical exome sequencing for 5 infants, whole exome sequencing for 4 infants, karyotype analysis on fibroblast for 1 infant. No further investigations were performed on 1 patient and 1 was enrolled in another study.



RESULTS

At the time of data analysis 6 investigations were completed with average time of 30 days. Three patients (50%) received a genetic diagnosis, with double diagnosis in one of them. Two analysis (33.3%) found variants in 2 new candidate genes. One analysis was negative. Clinical management changed in 4 patients (66.6%), 2 families received recurrence risk counselling and the brother of a proband had the same genetic diagnosis.

CONCLUSIONS

Our study provides strong evidences on the need to structure an "urgent" diagnostic path dedicated to critical infants with suspected monogenic disorders and confirms the clinical utility of Exome Sequencing for diagnosis in these patients with immediate impact on medical management, on family counselling and on the discovery of new disease genes.

PT	SEX	CLINICAL PICTURE	GENETIC TEST	RESULT	MANAGEMENT
P1	M	Chronic Diarrhea	Clinical Exome (trios)	SLC5A1: c.[722C>T];[1946G>A] Diagnosis: GLUCOSE/GALACTOSE MALABSORPTION	Diet therapy with resolution of clinical manifestations. Family Counseling for recurrence risk. Diagnosed the older brother.
P2	M	Facial Dysmorphisms, Congenital Heart Disease, Hypospadias, Clubfeet, Gastroesophageal Reflux, Generalized Hypotonia	Clinical Exome (trios)	ATRX: c.[727T>C] Diagnosis: α-THALASSEMIA/ MENTAL RETARDATION S. NKK2-6: c.[826G>T] Diagnosis: CONOTRUNCAL HEART MALFORMATIONS	Change in medical management Family counseling for recurrence risk.
P3	F	Diaphragmatic Hernia, Congenital Heart Disease, Left Clubfoot	WES (trios)	Composed heterozygosity in gene ALDH1A2 inherited from parents	Contribute to functional studies in the suspicion that it is a new disease gene.
P4	M	Cholestasis, Hepatosplenomegaly, Granulomatous Skin Lesions, Generalized Hypotonia	WES (trios)	NPC1: c.[736G>T];[2705C>G] (VoUS ,inherited from parents) NIEMANN-PICK D., TYPE C1	Specific clinical-instrumental follow-up.
P5	M	Facial Dymorphisms, Cleft Palate, Skeletal Contractures/Deformities, Hypotonia, Muscle Hypotrophy	WES (proband +mother)	ASCC3: c.[5281C>T];[4955G>A]	Clinical-instrumental follow-up in the suspicion that it is a new disease gene.
P6	F	Laryngo-tracheo-esophageal Cleft, Congenital Heart Disease	Clinical Exome	Negative	

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2. Meng L, et al. Use of Exome Sequencing for Infants in Intensive Care Units, Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. JAMA Pediatr. 2017;171(12):e173438. Doi:10.1001/jamapediatrics.2017.3438