Clinical Features and Follow-Up in Patients with 22q11.2 Deletion Syndrome

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Objective To investigate the clinical manifestations at diagnosis and during follow-up in patients with 22q11.2 deletion syndrome to better define the natural history of the disease.

Study design A retrospective and prospective multicenter study was conducted with 228 patients in the context of the Italian Network for Primary Immunodeficiencies. Clinical diagnosis was confirmed by cytogenetic or molecular analysis.

Results The cohort consisted of 112 males and 116 females; median age at diagnosis was 4 months (range 0 to 36 years 10 months). The diagnosis was made before 2 years of age in 71% of patients, predominantly related to the presence of heart anomalies and neonatal hypocalcemia. In patients diagnosed after 2 years of age, clinical features such as speech and language impairment, developmental delay, minor cardiac defects, recurrent infections, and facial features were the main elements leading to diagnosis. During follow-up (available for 172 patients), the frequency of autoimmune manifestations ($P = .015$) and speech disorders ($P = .002$) increased. After a median follow-up of 43 months, the survival probability was 0.92 at 15 years from diagnosis.

Conclusions Our data show a delay in the diagnosis of 22q11.2 deletion syndrome with noncardiac symptoms. This study provides guidelines for pediatricians and specialists for early identification of cases that can be confirmed by genetic testing, which would permit the provision of appropriate clinical management. *(J Pediatr 2014; ■: ■-■).*

Chromosome 22q11.2 deletion syndrome (22q11DS) (Mendelian Inheritance in Man [MIM] No. 611867), also known as velo-cardio-facial syndrome (MIM No. 192430), is one of the most common genetic syndromes with a prevalence of 1:4000 to 1:6000,[1,2] and possibly as high as 1:2000.[3] The syndrome has variously been labeled as DiGeorge syndrome (MIM No. 188400), velo-cardio-facial syndrome, cono-truncal-anomaly-face syndrome, Sedlačková syndrome, and, less frequently, Cayler cardiofacial syndrome.[4-8]

Microdeletions of the long arm of chromosome 22 at the q11.2 band are detected by fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, or array-based comparative genomic hybridization.

As is true for all microdeletion syndromes, inheritance is autosomal dominant, but most cases have a de novo 22 deletion.[9-11] The phenotypic spectrum is widely variable, with >190 features reported, including congenital heart disease, velo-

22q11DS	22q11.2 deletion syndrome
AIEOP	Italian Association of Pediatric Haematology and Oncology
MIM	Mendelian Inheritance in Man

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*A list of additional members of the Italian Network for Primary Immunodeficiencies is available at www.jpeds.com (**Appendix**).

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pharyngeal insufficiency and cleft palate, immune disorders, feeding difficulties, and hypocalcemia secondary to hypoparathyroidism.[3,12] The most common cardiac defects are conotruncal anomalies, including tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch.[13,14]

Despite the phenotypic variability, children with 22q11DS share a combination of features and have characteristic mild dysmorphic features, minor physical anomalies, or typical facial appearance (hypertelorism, hooded eyelids, tubular nose, broad nose tip, small mouth, and mild ear abnormalities). The main presenting features vary depending on the patient's age.[15,16]

The broad phenotypic spectrum of this syndrome requires multidisciplinary management of these patients.[17] However, there is limited information on the natural history of the disease and long-term outcome due to the lack of follow-up studies. Furthermore, clinical problems change over time and require different specialists, who might not always understand the complexity of the disorder. Here, we describe the results of an investigation of the presenting phenotype at diagnosis and follow-up of patients over time to better define the natural history of this 22q11DS.

Methods

In May 2005, Italian Network for Primary Immunodeficiencies and the Working Group of the Italian Association of Pediatric Haematology and Oncology (AIEOP) issued guidelines for management of patients with 22q11DS and invited through a questionnaire to register clinical data of patients in a secure database, compliant to International Conference on Harmonisation for Good Clinical Practice guidelines and European regulations. The AIEOP database registry is approved by the Ethical Committee of the reference center "Ospedale S. Orsola-Malpighi." From 2006 to 2012, 16 Italian centers from 10 of the 20 Italian regions have collected clinical retrospective end prospective data on 228 cases of 22q11DS and registered them in the database.

Clinical diagnosis was confirmed by fluorescence in situ hybridization 22 or molecular methods (multiplex ligation-dependent probe amplification 22 or comparative genomic hybridization microarray for 22q11.2 microdeletion) in all cases who presented with at least 2 of the following clinical features: congenital heart disease, palatal anomalies, neonatal hypocalcemia, recurrent infections/immunodeficiency and/or autoimmune disease, and characteristic facial features. Unavailability or lack of clinical features occurred for some specific variables depending on the sites reporting. Detailed information, consisting of personal data, family history, date of diagnosis, clinical manifestations, and treatment data, were collected in a structured questionnaire filled in at each center at the time of enrollment and on a yearly basis until 2012. All data have been stored in a central database at the AIEOP Operation Office and sent to the North-Eastern Italian Interuniversity Computing Center in Bologna.

Statistical Analyses

Participating centers were required to register all consecutive cases of 22q11DS, using a web-based database implemented at the North-Eastern Italian Interuniversity Computing Center in Bologna. Data were stored in a central database located at the AIEOP Operation Office.[18]

Standard statistical descriptions of variables were used to characterize the data (mean, median, and range). The Fisher exact test was used to compare differences in percentages for categorical variables, whereas the Student *t* test was adopted to compare means for continuous variables. Overall survival probability (±SE) was calculated both from the date of birth and from the date of diagnosis to the date of death due to any cause or of last contact, using the Kaplan-Meier method.[19] All *P* values were 2-sided and calculated among the same cohort of 172 patients. *P* values <.05 were considered statistically significant. Statistical analysis was performed using STATA (StataCorp, College Station, Texas).[20]

Results

Two hundred twenty-eight patients (112 males and 116 females) with a diagnosis of 22q11DS were included in the present study. The median age at diagnosis was 4 months (range 0-36 years 10 months, mean age 24 months). Prenatal diagnosis was made in 3 cases.

In 71% of patients (162/228), the diagnosis was made before 2 years of age: cardiac defects and neonatal hypocalcemia were the most relevant clinical features (**Table I**). The remaining 29% of patients (66/228) were diagnosed after 2 years of age (28% between 2 and 5 years, 36% between 5 and 10 years, 23% between 10 and 15 years, and 13% older than 15 years), and the clinical manifestations raising the suspicion of 22q11DS were speech and language impairment, development delay, and recurrent infections, associated with characteristic facial features (**Table I**). In 177 of 195 families (91%), neither parent was affected. The deletion was inherited from a parent in 18 of 195 families (9%); the mother had the deletion in 13 of 18 cases (72%) and the father in the remaining 5 (28%).

A congenital cardiovascular defect was confirmed in 172 of 219 subjects with 22q11DS (79%). In 103 of 186, cardiac defects led to diagnosis of the syndrome, and in most cases, this was established within the first years of life, except for 13 patients affected by minor cardiac anomalies (**Table I**). The most common major cardiac defect was tetralogy of Fallot in 37 of 172 cases (22%), followed by interrupted aortic arch type B, persistent truncus arteriosus, and aortic arch anomalies. Other cardiac anomalies were found in 109 cases and are described in **Table II** (available at www.jpeds.com).

Neonatal hypocalcemia was reported in 74 of 174 cases (43%), often associated with heart anomalies, although in 54 cases, information about possible neonatal hypocalcemia was not available. Hypocalcemia later in life and hypoparathyroidism were reported in 63 of 178 (35%) and 30 of 159 (19%) cases, respectively.