Clinical and psychomotor follow-up from 1990 to 2004 in 322 sicilian children with Down syndrome

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Abstract

Down syndrome is the most common identified cause of mental retardation. We have described clinical and psychomotor follow-up from 1990–2004 in 322 Sicilian children with Down syndrome. Medical management of the syndrome requires careful assessment, monitoring, prevention and vigilance.

Key-word: Down syndrome, follow-up

Introduction

Down syndrome (DS) remains the most frequent single cause of mental retardation. The prevalence at birth has recently decreased from one in 700 to about one in 1000. As a result of the changes in the practice of medical care, the life expectancy in DS has improved radically in the past few decades. The median age of death has increased and the average life expectancy in persons with DS has recently been prolonged to 49 years of age. Medical management of the syndrome requires an organised approach of assessment, monitoring, prevention and vigilance.

At the Paediatric and Intensive Therapy Department for the newborn of the University of Palermo 322 subjects (166 males and 156 females) from Sicily are under a follow-up programme from birth to 18 years of age. The follow-up consists of a periodic appraisal of the health of the DS child (auxological and psychomotor follow-up) and a clinical-diagnostic programme for recognising the diseases most frequently associated with DS (congenital malformations, autoimmune diseases, etc.).

It is therefore necessary to know the natural history of DS, the medical complications occurring and their prevalence at different ages.

Epidemiology

Both neonatal and infant mortality were significantly higher in the DS children than in the general population. The mortality has fallen in the past few years. Between 1978 and 1984 in Italy mortality occurred in the first month of life in 7.9% of the cases; out of 322 children with DS followed-up from 1990 to 2004, 14 (4.9%) died at various ages: 8/322 (2.5%) of congenital heart disease, 2/322 (0.6%) of leukaemia (one acute lymphatic leukaemia and one acute myeloid leukaemia), 3/322 (0.9%) of severe systemic infections and one (0.3%) of fetal hydrops.

Assessment and management (from birth to 18 years) (tab.1)

Clinical diagnosis and cytogenetic analysis

Although the phenotype is variable, a clinical diagnosis is possible at birth in most cases in relation to the characteristic physical features. Difficulties can arise in very small babies, as in the case with premature or small-for-age newborns, or if there are severe clinical problems that turn the attention away from the phenotypic characteristics of the infant. In our experience most cases 319/322 (99%) have been diagnosed in the first month of life. The chromosome analysis in 309/322 (96%) showed a standard trisomy 21 originating from a non-meiotic chromosome disjunction, in 9/322 (2.8%) a trisomy from unbalanced robertsonian translocation [of which the most frequent is the 14/21 and in 3/322, (0.9%) t21;21], xde novos in 78% of cases, and in 4/322 (1.2%) there was a mosaic trisomy with the presence of two cellular lines (cells with normal karyotype and cells with trisomy 21). In cases of translocations, the risk of having another newborn with Down syndrome is related to the occurrence in one of the parents of a balanced translocation.

Communication of the diagnosis

The communication of the diagnosis is, perhaps, the most delicate moment of the whole follow-up period of the child with Down syndrome and it must be done in two stages: when the diagnosis is suspected and when it is confirmed.

Clinical and instrumental investigations for congenital malformations

Congenital heart disease is the most common and severe malformation: about 50% of newborns are affected. In our experience congenital heart disease was found in 135/322 (42%) cases: in 55/135 (41%) atrioventricular septal defect, in 43/135 (32%) ventricular septal defect; in 16/135 (12%) secundum atrial septal defect, in 11/135 (8%) persistent patent ductus arteriosus, in 8/135 (6%) tetralogy of Fallot and in 2/322 (0.6%) other lesions.

All newborn babies with Down syndrome must be submitted to an echocardiogram by a paediatric cardiologist, even in the absence of symptoms. Congenital oral-gastrointestinal tract malformations were frequent (7.3%) in 322 Sicilian children with DS congenital gastrointestinal tract malformations were identified in 17 patients (5.2%). The most frequent anomalies were: duodenal stenosis in 4/322 patients (1.2%); congenital megacolon in 4/322 (1.2%); anal atresia in 3/322 (0.9%), oesophageal atresia in 3/322 (0.9%); cleft palate in 2/322 (0.6%) and diaphragmatic hernia in 1/322 (0.3%). Cryptorchidism was found in 28/166 (17%) males subjects.

Auditory screening

Since sensory defects are frequent in Down syndrome, all the newborns with Down syndrome must be submitted to investigations of the auditory ability (otoacoustic emission at birth and/or brainstem auditory evoked response at 3 months). In 4/322 (1.2%) congenital sensorineural deafness was discovered. A characteristic serous otitis can develop in the first years of life and can often persist throughout adulthood. A preventive approach to the hearing problems of children with DS seems therefore of the utmost importance in order to help them to acquire a good communication ability and satisfactory socialisation.

Ophthalmological disorders

Red reflexes should be checked at birth, as their absence is an important clinical sign of congenital cataract (15%). In the Sicilian chil-
dren with DS congenital cataract was found in 4/322 (1.2%) patients and a 15-year-old girl had acquired cataract. Nystagmus was identified in 64/322 subjects (20%), strabismus in 132/322 (41%) and refractive errors in 167/322 (52%) patients studied.

**Investigations for Hematological abnormalities**

During the neonatal period polycytemia (18%) (that should be treated in order to avoid cerebral damage), transient myeloproliferative disorder, thrombocytopenia, thrombocytosis, macrocytosis, lower or higher leucocyte count and congenital leukaemia(<1%) are frequent. In our experience polycytemia was found in 70/322 (22%) newborns while only 3/322 (0.9%) suffered from transient myeloproliferative disorder and there was one case of congenital leukaemia.

An increased risk of leukaemia in patients with DS has been systematically described and is now well documented. Hemogram, blood glucose examination and serum IgA, IgM, IgG levels should be checked annually. Liver and renal functionality and measurement of plasma lipid levels should be carried out when supported by anamnesis or clinical examination.

Out of the 322 children included in the study we found 7 cases of leukaemia (1.86%): 4 acute lymphatic leukaemia and 3 acute myeloid leukaemia. The median age of diagnosis was 3.2 years. Leukaemia in patients with DS occur mostly during the first years of life.

**Screening test for congenital endocrinological anomalies**

Congenital hypothyroidism is much more frequent than in the general population (1%)11. Screening for thyroid disease must be carried out at birth. In our experience congenital hypothyroidism was reported in 4/322 (1.2%) subjects with DS (3 male newborns and 1 female newborn).

There is an increased risk of acquired hypothyroidism (about 28%)13. Out of 311 children over 6 months of age we found subclinical hypothyroidism in 38/311 (12%) and autoimmune hypothyroidism in 40/311 (12.8%). The sex ratio was 2M:1F in both forms of acquired hypothyroidism. The median age at diagnosis was 6.2 years for subclinical hypothyroidism and 11.8 for autoimmune hypothyroidism. Appropriate substitutive therapy is recommended in congenital and acquired hypothyroidism. The cases with TSH levels between 11 and 20 mUl may benefit from treatment with low-dose thyroxine13.

Diabetes mellitus develops in at least 1% of children and adolescent with DS14. We
found only one case, but other two of the family were affected.

**Screening for celiac disease**

Celiac disease has an increased prevalence in DS, ranging from 4 to 17%\(^1\). After the first year of life the subjects are screened for celiac disease. 303 children over a year old included in the study, were screened for celiac disease using IgA and IgG antigliadin testing, IgA EMA; IgA and IgG anti-transglutaminase antibodies. 18/303 (5.9%) were positive on screening and an intestinal peroral biopsy confirmed the diagnosis. In all the subjects the celiac disease was silent. The median age at diagnosis was 4.8 years. The basic treatment of celiac disease is a gluten-free diet that leads to a complete recovery. A strong commitment and constant surveillance are required for patients, because compliance is often difficult to obtain. The sex ratio was 1M:1F. In 11 patients celiac disease and autoimmune hypothyroidism were both present.

**Orthopaedic controls**

Muscular and orthopaedic anomalies are well known in DS. Muscular hypotonia and joint hyperlaxity are almost constant. Flat foot, genu valgum and patella instability are the main causes of walking problems and even of severe static troubles such as scoliosis and cyphosis. In our experience 4/322 (1.2%) suffered from severe scoliosis which obliged them to wear a correction corset. All patients had flat feet. About 13% of subjects with DS have subluxation of the cervical spine but are asymptomatic. An additional 2% of individuals with DS develop signs and symptoms of spinal compression\(^1\). At 3 to 5 years X-rays should be carried out to discover eventual atlantoaxial instability or subluxation. The recommended method has been a lateral neck x-ray in neutral, flexed and extended positions. Diagnosis is confirmed by X-rays that demonstrate a distance of 4.5–5 mm between the anterior side of odontoid process and posterior margin of the anterior atlas arch\(^1\). In 27/195 (13.8%) subjects asymptomatic atlantoaxial subluxation was found. Management of subjects with symptomatic subluxation requires immediate stabilization and surgery must be taken into consideration. One case of congenital hip dislocation and one of acquired hip dislocation were found. In 2 patients patella instability was identified.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
<th>% in down syndrome</th>
<th>% in normal population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>135/322</td>
<td>42</td>
<td>0.4</td>
</tr>
<tr>
<td>Congenital oral-gastrointestinal tract malformations</td>
<td>17/322</td>
<td>5.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>28/166</td>
<td>17</td>
<td>3–5</td>
</tr>
<tr>
<td>Congenital sensorineuronal deafness</td>
<td>4/322</td>
<td>1.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>4/322</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>64/322</td>
<td>20</td>
<td>0.007</td>
</tr>
<tr>
<td>Strabismus</td>
<td>132/322</td>
<td>41</td>
<td>3–5</td>
</tr>
<tr>
<td>Polycytemia</td>
<td>70/322</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Transient myeloproliferative disorder</td>
<td>3/322</td>
<td>0.9</td>
<td>*</td>
</tr>
<tr>
<td>Congenital leukaemia</td>
<td>1/322</td>
<td>0.3</td>
<td>*</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>7/322</td>
<td>1.86</td>
<td>0.0033</td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>4/322</td>
<td>1.2</td>
<td>0.025</td>
</tr>
<tr>
<td>Acquired hypothyroidism</td>
<td>78/311</td>
<td>24</td>
<td>0.11</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>18/303</td>
<td>5.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Atlantoaxial subluxation</td>
<td>27/195</td>
<td>13.8</td>
<td>*</td>
</tr>
<tr>
<td>Seizure disorders</td>
<td>10/322</td>
<td>3</td>
<td>0.66</td>
</tr>
<tr>
<td>Periodontal disease</td>
<td>161/322</td>
<td>50</td>
<td>1–10</td>
</tr>
</tbody>
</table>

Tab. 2: Congenital malformations and acquired disease in 322 Sicilian children with DS

* Congenital leukaemia, atlantoaxial subluxation and transient myeloproliferative disorder are not found in normal population.

**Dental controls**

Dental anomalies are a common problem whose solution is not an easy task. Moreover, objective difficulties are found in examining and specifically treating children and adults with DS. A peculiar dental anatomy, developmental anomalies and malocclusion are frequent. In our experience gingivitis and periodontal disease are frequent (50% of cases).

**Neurological observation**

The frequency of seizure disorders in patients with DS is greater than in the general population\(^1\). Out of the 322 children included in the study 10 (3%) had had seizure disorders.

**Neuromotor and cognitive developmental**

Early intervention programs are designed to comprehensively monitor and enrich development, focusing on feeding, gross and fine motor development, language and personal and social development. Patients with DS frequently understand the spoken language better than they can express themselves verbally. In our cases the psychomotor delay was of a medium degree with most problems in the language and cognitive fields.

**Prevention of obesity**

Individuals with DS have reduced resting metabolic rates, which contribute to a higher frequency of obesity than in other subjects\(^1\). In our experience 9/322 (2.7%) patients with DS became obese as time went on. The use of growth charts for Sicilian children with DS\(^1\) is especially helpful in assessing whether an early weight-for-height growth pattern is abnormal. Practical advice, therefore, and good nutritional educations should be imparted to the family and by the family, associated with sports activities.

**Discussion**

Children with DS have benefited from the advances in medical care with a reduction in infant mortality.
The availability of accurate information on survival of DS is an important requirement for clinical management, health care service provision and genetic counselling. Tertiary prevention includes the evidence of complications in affected patients ( Tab. 2 ). In the specific case of DS patients, those preventive actions include early psychomotor stimulation, adequate paediatric handlings of acquired pathologies (acquired hypothyroidism, celiac disease, diabetes mellitus, atlantoaxial instability or subluxation, seizure disorders, etc.) and congenital pathologies (congenital hypothyroidism, congenital sensory-neuronal deafness etc.), the timely surgical correction of associated defects (congenital heart disease, congenital gastrointestinal tract malformations, congenital cataract etc.) and the effective acceptance by the community into its educational system and labour force.

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