[haematologica reports]
2006;2(10):14-15

The neonate with severe combined immunodeficiency

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Severe combined immunodeficiency (SCID) is a rare congenital defect of immunity that, if promptly diagnosed, can be cured by stem cell transplantation. The Pediatric Department of the University of Brescia is the national referent center for diagnosis and treatment of children affected by SCID. Since 1990 more than 100 affected children were admitted within the unit.

Common patterns of clinical presentation were within the first three months of life failure to thrive, enteritis, interstitial pneumonia. In our experience mean time from first clinical signs to diagnosis was 50 days, moreover it has been calculated that over the past 15 years in our country at least 3 affected children die undiagnosed. Diagnosis at presentation does not require second level blood tests, the disease can be easily detected by full blood count with differential where in all cases lymphocytes are absent or very low. Lymphocyte subpopulations analysis and T cell functional tests subsequently confirm the diagnosis. Over the past 10 years the molecular defect of most forms of SCID have been characterized (Figure 1). These data allow, in at risk families, prenatal diagnosis. In the last decade we have diagnosed and treated more than a hundred children affected by SCID (Table 1).

The presentation of the disease

Nearly a third of the children presented symptoms at diagnosis consistent with a typical pattern of the disease at birth: maternal engraftment. Infact, since there is physiological recirculation of maternal lymphocytes during the second trimester of pregnancy, in the cases where the foetus lack cellular immunity (SCID) engraftment occurs. Therefore the child at birth presents with cutaneous rash, hepatopathy, diarrhoea due to T lymphocyte maternal engraftment, that gives rise to a disease that is similar to graft versus host disease, the complication of donor/recipient incompatibility after bone marrow transplantation. In this cohort of children diagnosis could be difficult since apparently the number of T lymphocytes appear to be normal, with an activated phenotype, while full blod count do not suggest the presence of the disease. Once HLA typing is performed on lymphocytes a mixed chimera (feto/maternal) becomes evident with maternal T cells coexisting with fetal B cells. In these cases is sometime necessary administer an immunosuppressive therapy to the child, before bone marrow transplantation is performed, to minimize the clinical signs of maternal engraftment. Bone marrow transplantation is the treatment of choice with nearly 100% cure if a family matched donor is available, and 80% when the procedure is performed with a matched unrelated donor. Since the prognosis of the disease if correctly treated is good, the goal for the next year is therefore prompt diagnosis.

It is not uneven that as first signs of the disease as a newborn, a child could present with a severe form of clinical evident graft versus host disease after an unappropriate transfusion of a blood product. In our experience several affected children were transfused in the first periods of life in other institutions with blood products not irradiated; in all cases this gave rise to a potentially fatal GVHD. Lymphocyte typing demonstrates a chimeric state between the blood donor and the child.

In children who were referred to our centre from developing country is frequent a clinical presentation characterized by diffusion of BCG infection as a consequence of vaccination, that in several country is compulsatory. The signs are spread of the nodal involvement, cutanous manifestations, fever and malaise.

In western countries, on the contrary, due to sanification of waters, better life conditions, prompt use of antimicrobial, antimicotis and antiviral drugs in case of infections, diagnosis of SCID is often delayed after a clinical story of infections that sometimes are mild. It is not exceptional that diagnosis is posed at 8-12 months. In these cases prevalent symptoms are failure to thrive, interstitial pneumonia, intractable diarrhoea.

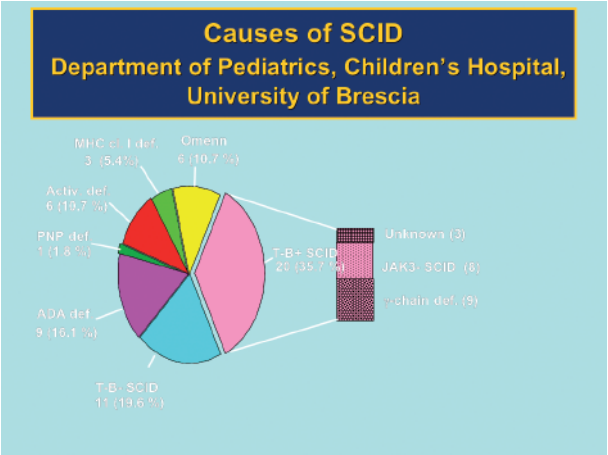

Figure 1. Causes of SCID.

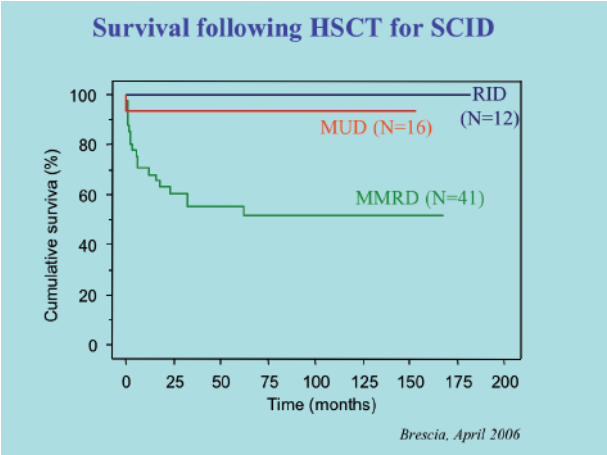

Figure 2. Survival following HSCT for SCID.

Table 1. Severe primary immunodeficiences.

Type of immunodeficiency	*No. of transplants*
Wiskott-Aldrich syndrome	21
Leukocyte adhesion deficency	6
Combined immunodeficiencies	8
SCID	107
ADA deficiency SCID	3
Hyper-IgM syndrome	4
Lymphohistiocytosis	8
Chediak-Higashi syndrome	2
Kostmann disease	1
IPEX	1
X-linked agammaglobulinemia	2
Chronic granulomatous disease	2

The treatment

Severe combined immunodeficiency is a fatal disease unless treated with stem cells capable of reconstituting a normal immune system. As soon as diagnosis is made, children affected must be kept in a complete isolation regimen in laminar ait flow room and the search for a donor must be immediately started. The best treatment results have been achieved by using family members donors who are HLA identical to the receipient. In our experience, if this is the case, the survival is approximately 90%. Most part of patients, nevertheless, do not have a matched family donor, matched unrelated donor (MUD) or haploidentical donor transplants must be considered. Recently we have published the data relative to BMT in SCID after MUD transplants in consecutive series of 94 children a reported a survival that exceeded 80%. In case of haploidentical transplants the survival is lower (between 50 and 60%) (Figure 2).

It is now evident that the BMT has better result if the child is transplanted as soon as possible after diagnosis, nevertheless still now in 2006 a recent report from the Italian Association of Pediatric Haematology and Oncology (AIEOP) demonstrates how time interval between first signs of SCID and diagnosis is 3,5 months and time interval between diagnosis and BMT is 3,2 months.

Future goals of the scientific community, as stated by a Consensus Conference organized by the European Council last June, is to avoid missed and/or delayed diagnosis that could expose to fatal consequences affected newborns that, if promptly grafted could survive the disease for good.

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