Project Title: PROMOTING EARLY DIAGNOSES IN NEUROMUSCULAR DISEASES: A FAST TRACK FOR PRIMARY CARE PEDIATRICIANS

BACKGROUND

Neuromuscular diseases (NMD) include a large number of rare, severely invalidating disorders of the nervous system, with a great variability of age of onset and clinical presentations, often with a multisystemic involvement. In the last decade, the knowledge on pathophysiologic mechanisms of neuromuscular diseases has dramatically expanded, leading to improved diagnostic techniques and opening the possibility of new therapies. Moreover, large-scale collaborative clinical studies have more precisely described the natural history of the different subgroups of diseases, resulting in the individuation of specific outcome measures to be utilized in the patients follow up and in new therapeutic clinical trials.

New standards of care have been produced with the consensus of the scientific communities for many groups of diseases, in order to optimize the timing of preventive interventions on a multidisciplinary ground, in particular for the pediatric age.

As a general conclusion, all the evidences strongly indicate that any type of treatment, both pharmacological and interventional, produce the best results only if they are started in the early phase of the diseases, when the very first symptoms or signs have appeared. This is particularly relevant in the pediatric age for the most invalidating forms of NMD and may have even a greater impact in the few diseases with specific drug therapies, such as Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA) and Pompe disease (PD).

The diagnosis of a NMD, especially in neonates and in small children, may be challenging, due to a very subtle onset of signs often disregarded by parents and by family doctors for months or years, until they are overtly manifested, missing the optimal timing of the therapeutical interventions

NMD are rare diseases, and they are not diffusely known among the health operators; moreover, in some cases the diagnostic process may be very complex and possible only in tertiary care settings. This explains the long diagnostic delay, still observed in all countries (Table 1. Diagnostic delay in some NMD)

Several consequences of a delayed or missed diagnosis may be considered. First, most NMD in the pediatric age are genetically determined, and a second or even a third birth of affected children in the same family may occur, if a genetic counselling is not promptly offered. Second, a delayed treatment may negatively influence the answer to the therapeutical strategies, weakening their

impact on the natural course. Third, the failure to recognize a disease which can be fruitfully treated in the due time may have legal consequences for the doctors.

Brief descriptions of DMD...

SMA...

PD....

AIM OF THE PROJECT

Aim of the project is to sensitize the community of Primary Care Pediatricians in the province of Torino to the early diagnosis of NMD, offering a 'fast track' to identify and promptly refer the suspected cases, in order to reduce the diagnostic delay

MATERIAL AND METHODS

This pilot study will involve n..... Primary Care Pediatricians operating in the five ASL in the province of Torino, accounting for about 2280000 inhabitants, with an estimated number of 16000 new births per year.

The study will be conducted for one year, based on the routine 'health controls' visits required by the National Health System schedule for each child from birth to three years (15 days, 3 months, 5 months, 8 months, 12 months, 18 months and 36 months).

For each control at different ages, few specific flags are inserted among the items already listed in the checklist currently utilized by the doctors, that are easily tested in the routine visit with no extra burden for the doctor.

For each colored flag, specific instructions are given, according the age of the patient and the clinical suspect, in order to rapidly identify those at risk for a NMD, with special alert for SMA, PD and DMD.

Four orders of interventions are considered:

1. RED FLAG: Direct referral to the coordinating Center, through a web-based form and after informing the parents that a second-level visit is required; the patient will be contacted by an operator, and a diagnostic process will be started according the standard protocols; if no NMD will be diagnosed, the patient will be addressed to the competent health service
2. ORANGE FLAG: hematological testing needed (i.e., CK and lactic acid levels) according specific instructions (i.e. CK > 500 → report to CC; CK 200-450 → retest, if persistent send to local NPI service; CK normal, retest in the next control)

3. YELLOW FLAG: doubt result, to be carefully retested in the next control or referred to the local NPI service
4. GREEN FLAG: no actions

FLOW CHART

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Specific didactic material and instructions will be distributed both by web-based courses and paper documents to facilitate the identification of suspected signs in the early stages of a NMD

EXPECTED RESULTS

Epidemiological data on NMD are difficult to verify, due to the rarity of the diseases and the expanding nosography, which complicate the exact count of patients. For DMD, the estimated incidence is 1 out of 5000 new male birth per year, that means 1 to 2 new cases per year on this considered population. SMA incidence is calculated 1:10000 new births per year, that means 1,6 cases per year; Pompe disease is rarer, with an incidence of 1: 40000.

The prevalence of all the other rarer NMD in childhood is not known, and it has globally calculated on the general population as 16.14 cases per 100.000 (= 370 cases, percentage of < 3 years not known)

The expected results will be:

1. Significant anticipation of the age at diagnosis: expected 1-3 months for SMA1 and IOPD; 6 months for SMA 2; 18-24 months for SMA III, DMD, LOPD
2. Potential earlier diagnosis of other NMD and neurodevelopmental disorders
3. Precise epidemiological data on pediatric NMD in the province of Torino

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