NEONATAL SCREENING FOR BIOTINIDASE DEFICIENCY

SUMMARY

Introduction: Neonatal screening programmes are a secondary prevention strategy that seeks to halt a disease's progression by ensuring early treatment in the presymptomatic stage and thereby improve its prognosis. Prior to implementing any neonatal screening programme, it is of the utmost importance to ascertain its efficacy, feasibility and cost-effectiveness by carrying out an assessment of the screening test, diagnostic confirmation tests, disease-management protocols and system used to evaluate the programme, which should, moreover, ensure adequate care at all screening stages. This assessment report was drawn up at the request of the National Health System Interterritorial Council's Services, Insurance & Finance Committee, in response to a proposal from the Galician Regional Health Authority.

Objectives: To assess existing evidence on the clinical effectiveness of neonatal biotinidase deficiency screening; and specifically, to analyse the incidence and/or prevalence, clinical characteristics and prognosis of the disease, as well as the screening test's analytical validity (sensitivity, specificity and predictive values) and benefits in terms of its effectiveness vis-à-vis morbidity and mortality.

Methods: Systematic review of the literature, covering the main biomedical databases (Medline, Embase, Cochrane Library Plus, HTA (Health Technology Assessment), DARE (Database of Abstracts of Reviews of Effectiveness), NHS EED (NHS Economic Evaluation Database), ISI Web of Science and *Índice Médico Español* (*IME*), among others). We used two search strategies -one centred on the epidemiology, clinical characteristics, morbidity, mortality, diagnosis and treatment of biotinidase deficiency, and the other centred on the screening of the disease- spanning the period 1 January 2009 to July 2013. After reading the abstracts of the papers retrieved, only those that met the pre-established inclusion/exclusion criteria were selected. The studies were then classified, and the data extracted and summarised in evidence tables.

Results and discussion: Of the total of 319 studies retrieved by the bibliographic search, 34 were finally included. All of these were observational in nature and furnished direct evidence in only some cases. Biotinidase deficiency is an autosomal recessive inherited metabolic disorder which stems from a congenital error in the metabolism of biotin, with a decrease in the serum levels of this vitamin. While estimated world-wide incidence is approximately 1:60 000 births, the estimated incidence in Europe stands at 1:47 486 births, with a mean prevalence of 1.6 cases per 100 000 population. Profound biotinidase deficiency (enzymatic activity in serum lower than 10% of mean normal activity) can cause hypotonia, convulsions, respiratory problems such as hyperventilation, laryngeal stridor or apnea, conjunctivitis, viral or fungal skin infections through a weakening of the immune system, ataxia, delayed development, sensorineural hearing loss and vision problems, such as optic atrophy. Clinical onset usually occurs between one week and 10 years of life, with a mean of 3.5 months. The great majority of children with profound biotinidase deficiency present with symptoms or are at risk of presenting with them if they are not treated. While partial deficiency (serum enzyme activity of 10%-30% of mean normal activity) may give rise to any of the above symptoms, these tend to be mild and occur in situations of stress, such as prolonged infections and fasting. The disease is diagnosed by determination of biotinidase activity in serum/plasma using quantitative methods, generally the colorimetric method. Molecular diagnosis, through analysis of specific mutations or complete

sequencing of the biotinidase gene, is useful for differentiating between children with profound biotinidase deficiency, those with partial deficiency and bearers of profound deficiency; most children with partial deficiency have the c.1330G>C (p.Asp444His) mutation. Insofar as methods were concerned, most neonatal screening programmes used the colorimetric test to measure biotinidase activity in blood spot samples dried on filter paper. Treatment was based on oral administration of biotin in its free form throughout the patient's lifetime. Symptoms were resolved by the treatment, with the exception of hearing loss, optic atrophy and delayed development, which are usually irreversible, particularly if a long time has elapsed between onset and commencement of treatment. Leaving aside the existence of false negative results, sensitivity would be 100%, specificity would come close to this percentage, and overall PPV for all studies reviewed would be 14.79%. The great majority of cases detected by neonatal screening programmes were found to asymptomatic at the date of diagnosis, and compliance with early treatment with biotin allowed for normal somatic and psychomotor development.

Conclusions:

- The evidence on the effectiveness of biotinidase deficiency screening programmes is of low quality and is based on observational-type studies, fundamentally case series. On the basis of this information, this inborn error of metabolism would meet all the requirements for its inclusion in a screening programme.
- Prior to implementing such a programme, however, an appropriate protocol would have to be drawn up that maximised the test' sensitivity and specificity, and -in particular- the analytes to be used, the specific cut-points for each population and laboratory, and, where applicable, the second-tier tests.
- Lastly, information systems would have to be set up which were based on pertinent, relevant and reliable results, and made it possible to assess whether the activities or processes undertaken within the context of the screening programme were tailored to health needs, not only from a population standpoint, but also from that of the health system. Such information would serve as an aid when it came to measuring the attainment of goals, setting of priorities and taking of decisions.