NEWBORN SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA. SYSTEMATIC REVIEW

SUMMARY

Introduction: The aim of neonatal screening is to ensure presymptomatic identification and early treatment of treatable congenital endocrine and metabolic disorders, in order to reduce morbidity-mortality and any possible impairments and disabilities associated with such diseases. Most of these disorders do not manifest themselves clinically at time of birth but, if they are not diagnosed and treated, they can have extremely serious clinical consequences. Even so, neonatal disease screening should in no case be initiated unless the advantages of early detection to the newborn are clearly defined and there are guarantees of adequate diagnosis, follow-up and treatment for all children detected by the health care system. Furthermore, all newborns in the target population must be assured of equitable and universal access, with correct information being supplied to parents to help them in decision-making. 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: The main objective was to assess both the efficacy/effectiveness and safety of neonatal screening of the classic form of congenital adrenal hyperplasia (CAH) and the analytical validity of the screening test (sensitivity, specificity and predictive values). As a secondary objective, the disease's incidence/prevalence, natural history, prognosis, morbidity-mortality and early treatment were also analysed. The end purpose was to address the screening principles contained in the "Population Screening Framework Document", which was drawn up by the Population Screening Board on behalf of all of Spain's Autonomous Regions (*Comunidades Autónomas*) and was approved by the Public Health Committee of the National Health System Interterritorial Council.

Methods: We conducted a systematic literature review, taking the 2004 Neonatal CAH Screening Report issued by the Galician Health Technology Assessment Agency (*avalia-t*) as reference. In accordance with the information needed to meet the report's designated objectives, two comprehensive searches of the scientific literature were made in the main biomedical databases (January and May 2014), including CRD (Centre for Reviews and Dissemination database), HTA (Health Technology Assessment), DARE (Database of Abstracts of Reviews of Effectiveness), NHS EED (National Health Service Economic Evaluation Database), Cochrane Library Plus, Medline and Embase, among others. Papers were selected according to a series of pre-defined inclusion/exclusion criteria, and the quality of the scientific evidence was assessed using the scale developed by the Oxford Centre for Evidence-Based Medicine.

Results and discussion: As with the 2004 report, the studies retrieved that updated the original report were descriptive studies having a moderate-low level of evidence. No randomised controlled clinical trial was located that directly assessed the efficacy and/or safety of CAH screening.

CAH falls within the group of autosomal recessive diseases, and refers to a family of inherited disorders of adrenal steroidogenesis which are due to deficiencies in any of the enzymes that intervene in the cholesterol to cortisol pathway. Five enzyme deficiencies have been described, with the most frequent being that of 21-hydroxylase (21-0H), which accounts for 90% to 95% of all cases of

the disease. Clinically, the disease appears in three different forms according to the degree of enzyme deficiency, namely: 1) classic salt-wasting CAH, which is the severest and most frequent of the classic forms (75% of those affected); 2) classic simple virilising CAH, which is the mild-severe form; and, 3) nonclassic or late-onset CAH, which is the mild form. Following adrenal crises in the salt-wasting forms, permanent brain damage, low cognitive scores and learning disability have been observed. This study exclusively assesses the classic CAH form.

Management of CAH is not simple, and clinical practice varies widely. Moreover, depending on the patient's age, it may be based on: 1) halting hypersecretion of adrenocorticotropic hormone (ACTH) and concomitant hyperandrogenism (treatment from birth); 2) preventing salt-wasting in cases of severe 21-OH deficiency associated with adrenal crises accompanied by blood salt loss or increased plasma renin activity; or, 3) surgical correction. It is a chronic disease that requires long-term treatment and is based on glucocorticoid and/or mineralocorticoid replacement therapy.

The initial screening test consists of quantifying 17-hydroprogesterone (17-OHP) in a neonate heel-puncture blood sample. Of the available analytical immunoassay techniques, Dissociation-Enhanced Lanthanide Fluorescent Immunoassay (DELFIA®) is predominantly used but yields a high percentage of false positives (FPs). To improve the parameters of sensitivity and specificity, most screening programmes stratify the 17-OHP cut points by gestational age or birth weight. To improve PPV and specificity, many programmes require a second analysis in the case of positive results: in such instances, the same analytical determination technique can be repeated in a new blood sample (known as recall or follow-up testing) or, alternatively, new techniques can be incorporated, such as fast liquid chromatography tandem mass spectrometry (LC-MS/MS) which obtains the profile of steroids other than 17-OHP in the initial blood sample (second-tier test). PPV values vary widely, with values ranging from 1% to 87% in protocols with follow-up testing. In 2-stage screening, one programme reported a rise in this value from 0.4% to 8%. The incorporation of second-tier testing shows inconclusive results, with one study reporting an increase in the PPV and another reporting no significant differences. This wide variability depends on the incidence of the disease and the false-positive management capacity of the screening programme. In general, the PPV was observed to be better in full-term than in premature newborns. Regardless of the screening protocol, the sensitivity and specificity values obtained were around 73%-100% and 100% respectively.

The cost-effectiveness studies retrieved failed to clarify whether the introduction of CAH screening was cost-effective. In terms of the scenarios analysed, it was felt that CAH screening would only be acceptable in the most favourable scenarios.

Conclusions:

- Classic CAH is an important health problem whose incidence in Europe ranges from 1:975 to 1:16,964 newborns, with the ratio for Spain estimated to be 1:16,441.

- Salt-wasting forms register a high morbidity-mortality if not treated in time. This form of the disease is potentially lethal, with the studies located reporting a mortality rate due to adrenal crises in unscreened newborns of 4% to 11.9%. Early diagnosis and treatment is crucial to prevent these crises, which can prove life-threatening and have irreversible *sequelae*, such as intellectual impairment due to brain damage. Hence, the screening priority is to detect such

cases before the appearance of clinical symptoms. Clinical diagnosis is more complicated in the case of males, since they do not present with ambiguous genitalia.

- Although 17-OHP analysis may be an effective tool for early detection of CAH, it is nevertheless a test with a high FP rate and with values that are difficult to interpret. The cut points used for this test by the various screening programmes varied widely and depended on different factors, such as method of analytical determination, antibodies used, gestational age, birth weight or sample date (postnatal age).

- Among other criteria, justification for CAH screening is based on the fact that early detection of the classic salt-wasting form (before clinical symptoms), followed by immediate treatment, can prevent adrenal crises and, by extension, the related mortality and morbidity. The studies retrieved were of moderate-low quality. Although screening is reported to be able to prevent mortality from salt-wasting forms, most of the studies furnish no data on this outcome variable or are based on hypothetical data which suggest that screening could prevent 74%-86% of the mortality due to this disease.

- Arguments in favour of screening are mainly based on:

  -preventing adrenal crises marked by potentially lethal saline loss and major irreversible sequelae;
  -there are fewer instances of hyponatraemia in newborns detected by screening versus those detected by clinical diagnosis;
  -preventing erroneous assignment of sex in girls with the simple virilising form;
  -preventing hyperandrogenisation through early diagnosis of the simple virilising forms; and,
  -reducing stress in the families of the children detected and time of hospitalisation thanks to early diagnosis.

- Arguments against screening point to a number of drawbacks:

  -there is poor evidence to indicate a reduction in morbidity-mortality and, moreover, it is of moderate-low quality;
  -the latency period of the salt-wasting forms is short, so that early clinical onset could occur in cases where screening results are delayed;
  -there is neither a standard protocol nor consensus as to the cutoffs for interpretation of the analytical test;
  -difficult interpretation of results due to cross-reactions, particularly among premature newborns;
  -low PPV of the DELFIA® analytical method, which entails unnecessary follow-up of a high number of FPs;
  -identification of asymptomatic patients, among whom the possible adverse effects of the treatment are unknown; and,
  -it does not identify all patients with moderate forms of classic CAH.

- Before any new metabolic disorder is implemented within the context of an already established neonatal screening programme, its feasibility in the light of available resources must be ensured in order to guarantee a quality programme that will afford coverage at all stages, including treatment.

- In the case of classic salt-wasting CAH, there must be no delay in early diagnosis before the possible onset of clinical signs and symptoms, to ensure that the neonate obtains the full benefit of screening in terms of a reduction in mortality and the irreversible *sequelae* of adrenal crises.