Newborn Screening for Endocrine Disorders: Belgian Experience with ZenTech s.a. devices

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12th ISNS 2021 — 10 - 12 November 2021 — Luxembourg Going Virtual

Abstract

Neonatal screening for congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) are two endocrine disorders commonly integrated in newborn screening programs worldwide. The screening is generally ensured by quantifying, respectively, TSH and 17-OHP in newborns' dried blood spots. In Liège area (Belgium), newborn screening is centralized in the Biochemical Genetics Laboratory (CHU of Liège), which uses the NEONATAL TSH Screening ELISA and NEONATAL 17-OHP Screening ELISA devices, both CE-marked and manufactured by ZenTech s.a.
The aim of the presentation is to show a feedback from a 3-year-long use of these devices, on more than 15,000 samples for each parameter. These data were used to assess the clinical performance of the devices (diagnostic sensitivity, diagnostic specificity, *etc.*) according to the UE 2017/746 regulation (IVD-R, Annex I).

Introduction

Congenital hypothyroidism is one of the most common preventable causes of mental retardation and is also the most common congenital disorder of childhood (Saran, 2019). Thus, newborn screening for CH is one of the major achievements of preventive medicine: it has largely eliminated the intellectual disability associated with this disorder through early diagnosis and treatment (Büyükgebiz, 2013; Ford and LaFranchi, 2014).
Congenital adrenal hyperplasia is a family of common endocrine disorders characterized by impaired adrenal cortisol biosynthesis with associated androgen excess. The most common (90–95%) is caused by 21-hydroxylase deficiency (Balsamo *et al*., 2020). Newborn screening for CAH has resulted in decreasing the morbidity and mortality associated with the most severe forms of these disorders (Held, 2020).
In Liège area, the Biochemical Genetics Laboratory (CHU of Liège) screens these two endocrine disorders with ZenTech devices.

Methodology

Sampling

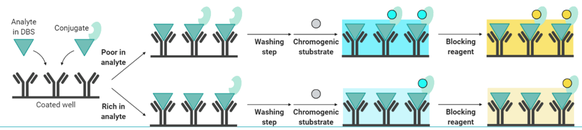
The trueness assessment was performed with spiked samples provided by the Centers for Disease Control and Prevention (CDC). The clinical performance is based on the results from newborn screening program performed at the Biochemical Human Genetics Laboratory (Liège, Belgium) from 1st January 2018 to 31st December 2020, representing a total of 46,592 samples. The neonates' blood sampling was generally done before the 7th postpartum day.

Principle of the assays

The NEONATAL TSH and 17-OHP Screening ELISA devices are intended to be used for the CH and CAH newborn screening, respectively. Both assays are based on colorimetric ELISA technique: the first is a sandwich ELISA, and the second a competitive one. Their principles are illustrated below.

NEONATAL TSH Screening ELISA

NEONATAL 17-OHP Screening ELISA



Measurement system

The measurement system is an ELISA automated system named Immunomat type 6381 (Virion Serion).

Statistical approach

The statistical method used is based on analytical and clinical performance defined in Article 9 of Annex 1 of the EU 2017/746 Regulation (IVD-R).

Results

NEONATAL TSH Screening ELISA

Analytical performance – Trueness

CDC samples (NSQAP)	Assessment	
	ZenTech	Expected
20201001001	Negative	Negative
20201001002	Negative	Negative
20201001003	Negative	Negative
20201001004	Negative	Negative
20201001005	**Positive**	**Positive**
20204001001	Negative	Negative
20204001002	Negative	Negative
20204001003	**Positive**	**Positive**
20204001004	Negative	Negative
20204001005	Negative	Negative

Clinical performance

Diagnostic sensibility and specificity, predictive values

	Disease present	Disease absent	
Positive test	17	232	PPV = 0.068
Negative test	0	46,343	NPV = 1.00
	Sensitivity = 100.00%	Specificity = 99.50%	

Likelihood ratios
LR += 200
LR −= 0

Expected values in affected and normal newborns' populations

	[TSH] (µUI/mL$_{blood}$)					
	N	Mean	Median	Min	Max	99th perc.
Affected	17	81.5	25.4	10.7	308.0	303.0
Normal	46,575	1.6	1.3	0.4	51.9	7.6

In the affected population, the lowest TSH levels were found mainly in newborns with transient CH or Down syndrome.

NEONATAL 17-OHP Screening ELISA

Analytical performance – Trueness

CDC samples (NSQAP)	Assessment	
	ZenTech	Expected
20204001001	Negative	Negative
20204001002	**Positive**	**Positive**
20204001003	Negative	Negative
20204001004	Negative	Negative
20204001005	Negative	Negative
20213001001	Negative	Negative
20213001002	**Positive**	**Positive**
20213001003	Negative	Negative
20213001004	Negative	Negative
20213001005	Negative	Negative

Clinical performance

Diagnostic sensibility and specificity, predictive values

	Disease present	Disease absent	
Positive test	7	245	PPV = 0.028
Negative test	0	26,662	NPV = 1.00
	Sensitivity = 100.00%	Specificity = 99.09%	

Likelihood ratios
LR += 109.9
LR −= 0

Expected values in affected and normal newborns' populations

	[TSH] (µUI/mL$_{blood}$)					
	N	Mean	Median	Min	Max	99th perc.
Affected	7	389.5	412.7	237.0	551.5	549.4
Normal	26,907	19.0	14.2	0.0	907.9	98.0

As expected, high 17-OHP levels were observed in the normal population, confirming the need to interpret the results in relation to GA, BW and stress factors (Anandi and Shalia, 2017).

Conclusions

The trueness evaluation of the NEONATAL TSH and 17-OHP Screening ELISA devices were based on DBS provided by the CDC. All the samples were correctly assigned, representing a 100%-match between the obtained and expected assessment.
Based on the Belgium 3-years experience, both devices presents good clinical performance. The NEONATAL TSH Screening ELISA diagnostic sensitivity and specificity are above the values found in the scientific literature (96.5% and 99%, respectively) (Saleh *et al.,* 2016; Knowles *et al*., 2018).
For the NEONATAL 17-OHP Screening ELISA, the clinical performance meets also the literature reference values *i.e.,* diagnostic sensitivity of 100%, diagnostic specificity of 99.8% and a positive predictive value of 0.011 (Heather *et al*., 2015).
Moreover, both devices provide credible diagnostic accuracy since the positive likelihood ratio is above 10 and the negative one is less than 0.1 (Deeks, 2001).

References

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Abbreviations: PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR: Likelihood Ratio; GA: Gestational Weight; BW: Birth Weight

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