CONGENITAL MALFORMATIONS, DYSMORPHIC SYNDROMES AND NEURODEVELOPMENTAL PROBLEMS IN CHILDREN WITH CONGENITAL HYPOTHYROIDISM

Gkini M.[1], Gkika A.[2], Iliadi A.C.[1,2], Platis D.[2], Giogli V.[2], Tataropoulou K.[1], Paltoglou G.[1], Kogia C.[1], Karagiannis A.[1], Chrousos G.[1], Girginoudis P.[2], Kanaka-Gantenbein C.[1], Voutetakis A.[1]

[1] Division of Endocrinology, Metabolism and Diabetes, 1st Department of Pediatrics, "Aghia Sophia" Children's Hospital, Athens University School of Medicine [2] Department of Biochemistry, Institute of Child Health

Background knowledge

A high frequency of extra-thyroidal congenital anomalies has been reported in infants with congenital hypothyroidism (CH) detected by neonatal screening. Current ESPE guidelines recommend that congenital malformations, underlying dysmorphic syndromes and psychomotor and language development should be sought for and monitored in CH patients. The identification of co-existing nosologies and malformations is helpful not only for clinical purposes but also for uncovering the underlying genetic defects of CH.

The **National Greek Neonatal CH screening program** was initiated in 1980 and is carried out by a **single laboratory** that receives and tests the Guthrie cards from all the maternity hospitals in Greece. Over the last 35 years, more than **3,690,000 neonates** have been screened.

Objective and hypotheses

To record pathological conditions, malformations, dysmorphic features and syndromes and neurodevelopmental problems in children with CH diagnosed through the Greek neonatal screening program.

Patients and Methods

Data from the medical records of children diagnosed with CH through the Greek Neonatal CH screening program and followed by the Endocrine Division of the 1st Pediatric Department (Univ. Of Athens), were retrospectively analyzed (**n=435**). Certain data (e.g., ultrasonographic data of heart or kidney) were not available in all patient.

Results

Data of 435 patients (54,7% boys and 45,3% girls) were analyzed (**Table 1** and **Figure 1**). Of these patients, 11,5% were born after in vitro fertilization (IVF) and 25% were premature (<37 weeks). Thyroid dysgenesis was present in 17,7% of patients. Umbilical hernia was present in 12,2%, prolonged jaundice in 43,4%, cryptorchidism or retractile testes in 17,2% of boys (surgery in n=5). 13,8% of patients demonstrated a delay in speech or/and in motor development and speech therapy was necessary in 9,4%. Mental retardation was diagnosed in 3.9% of patients (n=9), none of which is CH-related (7 patients have Down syndrome and 2 are extreme prematures with severe related complications). Nevertheless, screening for intellectual disabilities was not universally applied. Autism was diagnosed in 2 patients. Severe hearing problems were documented in 4 patients. Of patients with pertinent U/S data, 5% had unilateral renal agenesis (n=5) and 8.9% had severe heart defects (n=9). Imaging data from specific patients are depicted in **Figure 2**. Dextrocardia with situs inversus was found in one CH patient who also had thyroid gland size in the low normal limits. Interestingly, his brother has thyroid dysgenesis.

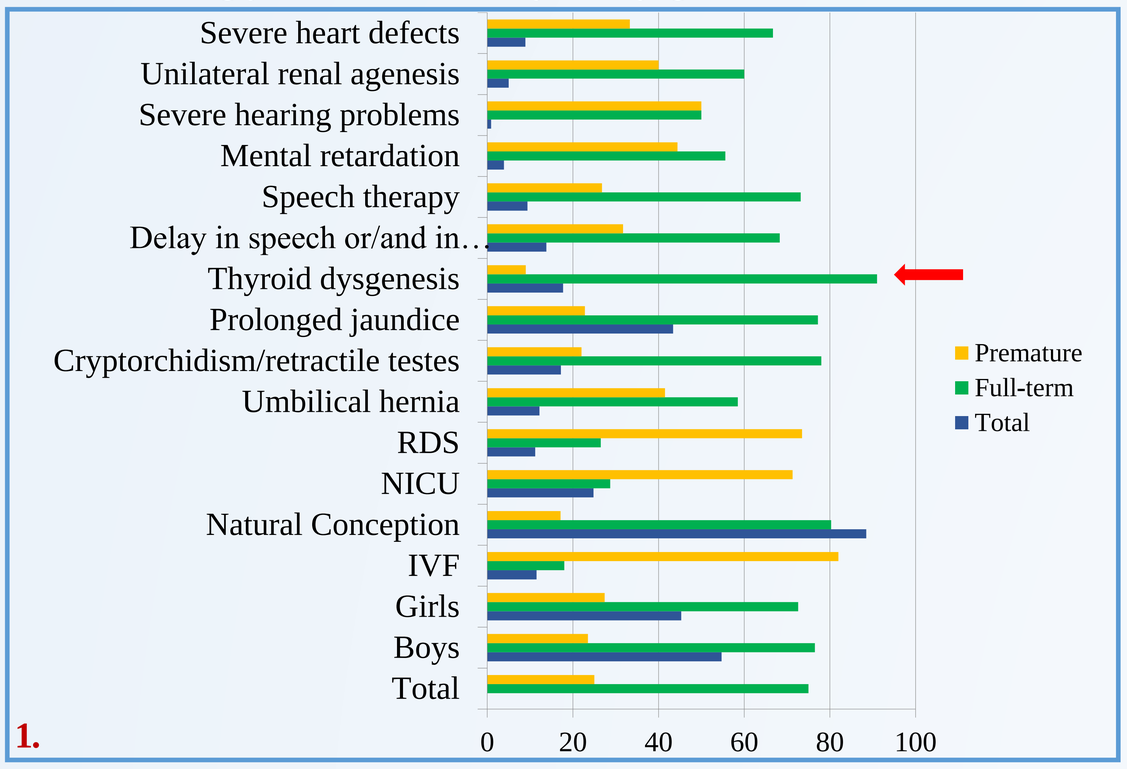

Figure 1: Incidence of defects in CH patients. Percent with respect to **Total (blue columns)** as well as percent of **full-term (green columns)** and **premature (yellow columns)** within each subgroup is depicted. Low incidence of thyroid dysgenesis in premature children is evident (**red arrow**).

Table 1	Total	Full-Term			Premature		
		Total	IVF	NC	Total	IVF	NC
Entire Cohort	435	**325 (75)**	9 (3)	309 (97)	**109 (25)**	41 (38)	66 (62)
Boys	238 (54,7)	**182 (56)**	5 (55,6)	174 (56,3)	**56 (51,4)**	22 (53,7)	33 (50)
Girls	197 (45,3)	**143 (44)**	4 (44,4)	135 (43,7)	**53 (48,6)**	19 (46,3)	33 (50)
IVF	50 (11,5)	**9 (2,8)**			**41 (37,6)**		
Natural conception (NC)	385 (88,5)	**309 (95,1)**			**66 (60,6)**		
Neonatal ICU	108 (24,8)	**31 (9,5)**	0 (0)	31 (10)	**77 (70,6)**	36 (87,8)	39 (59,1)
RDS	49 (11,2)	**13 (4)**	0 (0)	13 (4,2)	**36 (33)**	18 (43,9)	17 (25,8)
Umbilical hernia	53 (12,2)	**31 (9,5)**	0 (0)	30 (9,7)	**22 (20,2)**	8 (19,5)	14 (21,2)
Cryptorchidism or retractile testes	41 (17.2)	**32 (17,6)**	0 (0)	31 (17,8)	**9 (16,1)**	4 (18,2)	5 (15,2)
Prolonged jaundice	189 (43,4)	**146 (44,9)**	4 (44,4)	138 (44,7)	**43 (39,5)**	18 (43,9)	24 (36,4)
Thyroid dysgenesis	77 (17,7)	**70 (21,5)**	1 (11,1)	69 (22,3)	**7 (6,4)**	1 (2,4)	6 (9,1)
Delay in speech or/and in motor development	60 (13,8)	**41 (12,6)**	1 (11,1)	39 (12,6)	**19 (17,4)**	4 (9,8)	15 (22,7)
Speech therapy	41 (9,4)	**30 (9,2)**	1 (11,1)	29 (9,4)	**11 (10,1)**	3 (7,3)	8 (12,1)
Mental retardation	9 (3,9)	**5 (1,5)**	0 (0)	5 (1,6)	**4 (3,7)**	2 (4,9)	2 (3)
Severe hearing problems	4 (0,9)	**2 (1,2)**	0 (0)	2 (0,6)	**2 (1,8)**	0 (0)	2 (3)
Unilateral renal agenesis (in n=97)	5 (5)	**3 (4,7)**	0 (0)	3 (4,9)	**2 (6,1)**	0 (0)	2 (10,5)
Congenital heart defects (in n=101)	9 (8,9)	**6 (8,9)**	0 (0)	6 (9,1)	**3 (8,8)**	0 (0)	2 (9,1)

Table 1: Overview of the entire CH cohort. Number of patients with specific defect (% for sub-group in parenthesis) is depicted for Full-term and Premature patients as well as for type of conception (IVF or Natural). In the general population, estimated incidence for congenital hearing loss is 0.1%, unilateral renal agenesis is 0.03%, and congenital heart defects is 0.6-1.3%.

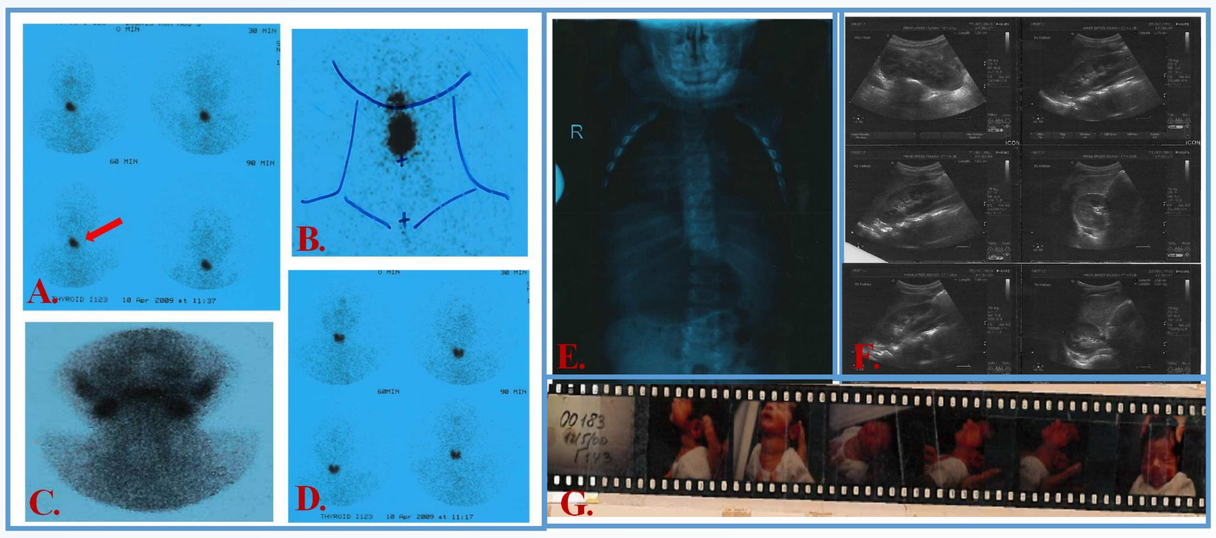

Figure 2: Thyroid scans depicting **(A)** Left hypoplastic thyroid lobe, **(B)** Ectopic sublingual gland, **(C)** Absence of thyroid gland and **(D)** Normal thyroid gland**. (E)** X-ray showing Dextrocardia with Situs Inversus in a CH patient. **(F)** Ultrasound showing left ectopic kidney in pelvis. **(G)** Newborn with goiter due to thyroid dyshormonogenesis.

Conclusions

Data indicate that thorough physical examination, follow up and a structured diagnostic workup is necessary in children with CH for prompt recognition and appropriate management. No differences were found between Full-term and Preterm newborns with respect to the incidence of severe extra-thyroidal defects.

Acknowledgments

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