Research Article

Delayed Diagnosis of Congenital hypothyroidism of Diverse Aetiology in Pakistan. An Experience from a Tertiary Care Hospital

Muhammad Ali[1] , Taeed Ahmed Butt[2] , Akmal Laeeq Chishti[3] , Zulqurnain[4] , Shan Elahi[5]

[1]Sahara Medical College, Narowal / Mayo Hospital, Lahore; [2]Fatima Memorial Hospital, Lahore; [3]Mayo Hospital, Lahore [4-5]Center of Nuclear Medicine (CENUM), Mayo Hospital, Lahore.

Abstract:

Background: Thyroid Disorders represent the most common endocrinopathy in childhood and a preventable cause of growth delay and mental retardation. Clinical manifestations of hypothyroidism are highly variable depending upon etiology, duration, age and severity. True incidence of congenital hypothyroidism in Pakistan is unknown due to lack of community surveys and long awaited national newborn screening program for hypothyroidism.

Objective: We aimed to determine the various etiological factors involved in the development of congenital hypothyroidism (CH) in cases coming to a tertiary care center. We also aimed to study the varied clinical presentation of congenitally hypothyroid cases to appreciate early detection and prompt diagnosis.

Methodology: This was a descriptive cross-sectional study conducted in the Endocrine Section of Department of Pediatrics, Mayo Hospital, King Edward Medical University (KEMU), Lahore, from July 2012 to January 2019. A predesigned proforma was used to record clinical and biochemical parameters of the Patients. The diagnosis of CH was based on clinical, radiological, and biochemical features.

Results: Out of 198 cases of permanent CH, 58.6% (116/198) were female. Among study patients, 33% (66/198) were under the age of 3 years, 32.2% (64/198) aged 3-11 months and 19.7% (39/198) between 1 - 3 years of age. The common clinical features at presentation were constipation 56.6%, unusual facies 53%, learning difficulties 42.4%, mental retardation 39.4%, short stature 38% and goiter 25.8% patients. Regarding aetiology, hormonal dysgenesis (56.5%) and iodine deficiency (26.6%) were found to be the common underlying factors. The association between age at diagnosis with various variables was computed using the Pearson chi-square test. P-value less than 0.05 was taken as statistically significant.

Conclusion: The high prevalence of iodine deficiency among Patients of CH points towards variable aetiology and importance in community health. The study also emphasizes the need to explore clinical features at different age groups, which help in establishing early diagnosis of CH in the absence of national neonatal screening programs in Pakistan.

Corresponding Author | Dr. Muhammad Ali, Visisting Faculty Paediatric Endocrine & Diabetes, Mayo Hospital Lahore/ Professor of Paediatrics Sahara Medical College, Narowal **Email:** mali-dr@hotmail.com

Keywords: Congenital hypothyroidism CH, iodine deficiency

Introduction:

Disorders affecting the thyroid gland represent the most common endocrinopathies in childhood and a preventable cause of growth delay and mental retardation.[1] Thyroid Hormone is principally involved in the growth, metabolism, and mental development of

children.[2] Reduced production of TH is the central feature of the clinical state, termed hypothyroidism. Acquired Hypothyroidism is less common as compared to CH in children, especially in iodine-deficient populations.[3,4]

The clinical manifestations of hypothyroidism are highly variable, depending upon its etiology, duration, age, and severity. The spectrum extends from sub-clinical to overt hypothyroidism to myxedema coma. Similarly, the age of presentation also varies between the cases presenting in childhood with hypothyroidism, dyshormonogenesis ,with normal clinical and biomarker presentation at birth to severe Hypothyroism at birth in athyrosis.[3]

Delayed diagnosis of this hormonal deficiency leads to irreparable damage to the physical as well as mental growth of the children.[5] Whereas, mental development may be normal in some Patients of CH like thyroid ectopy and dyshormonogenesis as compared to Patients with athyrosis.[6] As revealed in a study; mental development was found to be normal in 56% of CH patients, higher percentage (81%) being in patients diagnosed under 3 months of age than those diagnosed later in life (47%).[7] Furthermore, males compared to females have a higher risk of developmental delay as well as mental retardation.[8]

Pakistan lacks a national program for newborn hypothy-roidism screening, however, it is being carried out at certain tertiary care hospitals both private and public sector at a limited scale. Consequently, delayed clinical presentation and lab diagnosis are plausible reasons behind variable clinical features reported in local Pakistani data as compared to those in developed countries.

Congenital hypothyroidism is estimated to occur in 1 in 700 to 4000 children worldwide.[5,9] True incidence of CH in Pakistan is not known. A study from a tertiary care hospital of Karachi reported the incidence of CH as 1:1000 which was 4 times higher compared to developed countries.[9]

The prevalence of thyroid dysfunction in a community depends on gender, age, ethnicity, geographical background, and environmental factors especially iodine deficiency. For a long time, iodine deficiency was considered the most common cause of hypothyroidism until the adaptation of the universal salt iodination program.[10-11] The prevalence rate of congenital hypothyroidism among children in the developed world is estimated to be 1 per 2,372 versus 1 per 357 in developing Country like Iran.[12-13] Therefore, data of thyroid disorders from one population cannot be extrapolated to others.[13]

This study was conducted to find out the true etiology of CH in the Pakistani population and to identify various clinical features associated with CH at different ages of presentation. Understanding variable symptomatology at presentation will help in early suspicion of CH in local settings till a national neonatal screening program is implemented.

Methods:

This cross-sectional study was conducted in the Endocrine, Diabetes and Metabolism Section of the Department of Pediatrics, KEMU / Mayo Hospital, Lahore, from July 2012 to January 2019 after ethical approval from the Institutional Review Board of King Edward Medical University, Lahore (No 48330-Progect No14/13 Dated: 28-11-2012). After taking informed parental consent, 224 patients of CH were recruited by nonprobability consecutive sampling technique. This included all children already diagnosed as CH and on regular follow-up in Endocrine, Diabetes and Metabolic Clinic, Pediatrics department, along with newly diagnosed patients of CH during the study period as per inclusion criteria.

A predesigned proforma for clinical and biochemical parameters was used in data collection. The demographic and clinical parameters included family history, birth history, neonatal history, signs and symptoms at time of presentation (during neonatal and pediatric age) in suspected patients.

The age-specific (neonatal and pediatric) detailed examination for signs of hypothyroidism was done. The developmental assessment was carried out in developmental clinic and problems of developmental delay, mental retardation or physiological developmental delay {i.e. failure to thrive, delayed milestone, or short stature} were identified.

Each suspected patient was first investigated for thyroid

status (Free T4, TSH) and bone age (Gruilich Pyle method), for diagnosis and confirmation of Congenital Hypothyroidism.

The diagnosis of hypothyroidism was based on clinical, radiological, and biochemical parameters. The biochemical and radiological features included decreased FT4 (<11.5pmol/L) and raised TSH (>50mlU/L) levels alongwith delayed bone age > 2.5 SD from chronological age.

The first step was to establish whether CH was permanent or transient. Two parameters were used. In patients <3 years of age, fluctuation of TSH values (>10 mIU), on the variation of dose during treatment was taken. In patients >3 years of age, deranged thyroid profile, after stopping treatment for 6 weeks was taken.[14] To differentiate between congenital and acquired hypothyroidism, anti-thyroglobulin antibodies were measured and interpreted. Other antibodies involved in autoimmune hypothyroidism were not checked because of cost issue.

The etiological diagnosis of CH was made according to Algorithm (Figue I). Ultrasonography of the neck / thyroid gland and a thyroid scan were obtained in patients (newly diagnosed within 48 hours, before starting treatment, and in those on treatment after 3 years of age, after 6-week stopping treatment) in order to locate position of thyroid gland. Thyroglobulin level was determined for the presence of thyroid tissue and deficiency of iodine {Normal range of 4-40 micro-grams, excess (>40 microgram) indicates iodine deficiency}.[17] The modified perchlorate test was done for dyshormonogenesis.[6]

The sample size of the study was calculated with the help of open-source sample size calculator "Open-epi" using the prevalence of dyshormonogenesis (47.8%) as an etiological factor for CH.14 At 95% confidence level and bound by the error of seven, the sample size of 198 was calculated for this study.

The data were analysed using SPSS version 26 For qualitative variables, frequency and percentage were calculated, whereas quantitative ariables were computed as mean (SD). The association between age at diagnosis with various variables was computed using the Pearson chi-square test. P-value less than 0.05 was taken as statistically significant.

Results:

In this study, 224 patients were initially enrolled for congenital hypothyroidism; however 26 participants were excluded because 11 Patients could not be followed optimally to reach a final etiological diagnosis for various reasons. Nine patients were diagnosed as transient CH, and 6 Patients were found to have Thyroid antibodies on screening and thus excluded.

Out of 198 patients, 116 (58.6%) were females. Most patients 37/198 (67.7%) belonged to province of Punjab. Parental consanguinity was found in 49.5% patients (98/198). The mean (SD) parental age was reported as 41.64 years (+8.51) for fathers and 38.15 (+11.9) years for mothers. The minimum reported age at the time of diagnosis of CH was 8 days with maximum age at 19 years. Among study patients, 36.4% (72/198) were delivered at hospital, while rest were delivered at home. Regarding gestational age, 65% (129/198) were full term while 3% (6/198) and 2.5% (5/198) were born either premature or post mature (Either record/ recall). Six percent patients (12/198) weighed <1500gms at birth while 41% (81/198) weighed between 1500 to 2500 grams and 12% (24/198) patients were >2500 grams. Thirty-three percent (66/198) participants were diagnosed at the age >3 years and 32.2% (64/198) at 3-11 months, followed by 19.7% patients (39/198) at 1 to 3 years and 14.6% patients (29/198) diagnosed at <3 months age respectively.(Table-1)

In majority of study patients, no treatment gap (time of diagnosis & start of treatment), was found (119/198-60%).Only 11 % patients (22/198) had treatment gap, with maximum gap of 3 year (<1month to 3 yr).

Family history for hypothyroidism was present in 31.3% (62/198) patients, followed by hyperthyroidism in (3.5%, 7/198) and autoimmune disorders in 2% patients (4/198). A positive association was observed between family history and hypothyroidism. (Table-1)

Typical facies were reported in 23.2% patients (46/198). Two patient (2/198) of trisomy and one patient of Down syndrome were observed. The midfacial anomaly was found in 5.6% patients (11/198) while 25.8% patients (51/198) were found to have goiter.

Table 1: *Socio-demographics and Baseline characteristics of study cases (n=198)*

Characteristics	Value : n(% age)
Sex	
Male	82 (41.4)
Female	116 (58.6)
Ethnicity*	
Punjab	134(67.7)
Sindh	1 (0.5)
Pashtun	9 (4.5)
Others	3 (1.5)
Unknown	51 (25.8)
Twins	5 (2.5)
Consanguinity	98 (49.5)
Parental Age, mean (SD)	
Mother Age	38.15 (11.9)
Father Age	41.64 (8.51)
Age at diagnosis	
<3 months	29(14.6)
3-11 months	64(32.2)
1-3 years	39(19.7)
>3 years	66(33.3)
Treatment gap**	
<1 month	3(1.5)
1-5 months	8(4)
6-11 months	3(1.5)
1-3 years	3(1.5)
>3 years	5(2.5)
No gap	119(60.1)
Missing Data	57(28.8)
Family History	
Hypothyroidism	62(31.3)
Hyperthyroidism	7(3.5)
Autoimmune Disorder	4(2)

*Ethnicity data was missing for 51 participants
** Treatment gap data was missing for 57 participants

Twelve patients (6%) were having abnormal hair distribution. The umbilical hernia was noted in 9.1% patients (18/198). At presentation, most common symptom was constipation (56.6%, 112/198), followed by learning difficulties (42.4%, 84/198), mental retardation (39.4%, 78/198), and short stature in 38% patients (75/198). (Table-2)

On developmental screening, 40.4% patients were having normal development (80/198), global delay in 32.3% patients (64.198), and learning difficulties/poor school performance in 27.3% Patients (54/198).

Table 2: *General Clinical Features in study cases at presentation (n=198)*

Variables	Value : n(% age)
Dysmorphic Facial Features	
Typical Facies	46 (23.2)
Atypical	105 (53)
Not Assessed	47(23.7)
Associated Syndromes	
Trisomy	2(1)
Down syndrome	1 (0.5)
Mid Facial Hypoplasia	11 (5.6)
Goitre	51 (25.8)
Hairs distribution	
Normal	112 (56.6)
Abnormal	12 (6.1)
Not Assessed	74 (37.4)
Hypertrichosis	3 (1.5)
Brittle nails	9 (4.5)
Umbilical Hernia	18 (9.1)
Dental defects	9 (4.5)
Main Complaints at Initial Presentation	
Short stature	75 (37.9)
Mental retardation	78 (39.4)
Constipation	112 (56.6)
Hearing Impairment	15 (76)
Learning difficulty	84 (42.4)
Hyperactivity	14 (7.1)

Hearing assessment (By Audiometery) was done in 62.6% patients (124/198) and hearing impairment was found in 7.2% patient (9/198); this was followed by hypotonia in 12% patients (24/198), ataxia in 14% patients 7/198) and dysarthria in 6% patients (12/198). On detailed Clinical Examination Common developmental defects found were ventricular septal defects (9.55 % patients (9/198), atrial septal defect ASD in 9.25% patients (5/198) and bifid epiglottis in 2% patients (4/198). Associated medical conditions include Type 1 Diabetes 4.5% patients (9/198), celiac disease 3% patients, 6/198) and thalassemia 3% patients (6/198). (Table-3)

Figure-2 summarizes the association between age at diagnosis with developmental abnormatlity, autism, ataxia, and mental retardation.

Regarding the etiology of CH, primary CH was found in 92.9% of patients (184/198), while Central CH in 7% of patients (14/198). Among Primary CH, Dysgenesis

Table 3: *Developmental defects and assessment among study cases (n=198)*

Variables	Value : n(% age)
Development Assessment	
Global delay	64(32.3)
Normal development	80(40.4)
Learning difficulty/ Poor School Performance	54(27.3)
Clinical Examination	
Ataxia	14(7.1)
Hypotonia	24(12.1)
Hypertonia	9(4.5)
Dystonia	1(0.5)
Spastic Quadriplegia	2(1)
Nystagmus	6(3)
Dysarthria	12(6.1)
Autism	10(5.1)
Delayed Reflexes	10(5.1)
Hyperreflexia	7(3.5)
Hypertrichosis	5(2.5)
Precocious puberty	6(3)
Microphallus	1(0.5)
Hearing	
Impaired	9(7.2)
Normal	115(92.3%)
Development Defects	
Bifid Epiglottis	4(2)
Cleft Palate	3(1.5)
Choanal Atresia	3(1.5)
Ventricular Septal Defect	9(9.5)
Atrial Septal Defect	5(2.5)
Associated Ailments	
Type 1 diabetes	9 (4.5)
Celiac	6(3)
Thalassemia	6(3)
Cold nodules	2 (1)
Down syndrome	2 (1)
Epilepsy Verbal slowing	1(0.5)
Hirschsprung's Disease	1(0.5)
Mental delay	1(0.5)
Psychiatric illness	1(0.5)
Pulmonary Tuberculosis	1(0.5)

was reported in 56.5% patients (104/184). Among them (Dysgenesis), Hypoplasia was reported in 77.9% patients (81/104), Ectopic 18.2% (19/104), majority lingual ectopic gland in 89.4% (17/19), followed by Athyrosis in 3.8% (4/104). Dyshormonogenesis was found in 14.1% patients (26/184), whereas iodine deficiency-induced CH was reported in 26.% patients (49/198). Cold nodules were found in 2.7% patients (5/184). (Table 4)

Table 4: *Etiology of Hypothyroidism among study cases (n =198)*

Variables	Value : n(% age)
Etiology n (%).	
Central	14 (7 %)
Primary	184 (92.9 %)
Dysgenesis	104 (56.5 %)
Athyrosis	04 (3.8 %)
Hypoplasia	81 (77.9 %)
Ectopic	19 (18.2%)
Ligual	17 (89.4 %)
Sublingual	02 (10.5 %)
Iodine Deficiency	49 (26.6 %)
Dyshormonogenesis	26 (14 .1%)
Cold Nodule	05 (2.7 %)

Discussion:

In an iodine-deficient country like Pakistan, the true etiology of CH is unknown. Therefore, the results of this study are not only useful for identifying the etiology of CH but also emphasize on the role of various clinical features in the early detection of CH in the absence of national neonatal screening program for CH, in developing countries.

According to results, CH was more prevalent among females. This is consistent with the results of Rezaeian et al as having females at higher risk of having CH.[15] Other studies have suggested an equal female to male ratio.[16] DeMartino et al had found male gender to constitute 64% of infants being screened at birth for CH.[18]

Consanguinity has been observed as common association in CH. A study conducted in Iran had reported a significant association between CH and parental consanguinity (P= 0.006). This study relates a high prevalence of consang-uinity due to a high rate of thyroid dysgenesis.[19] Parental consanguinity was noted among half of the study cases.

The early identification and timely management of CH are crucial for the child's optimum mental growth and

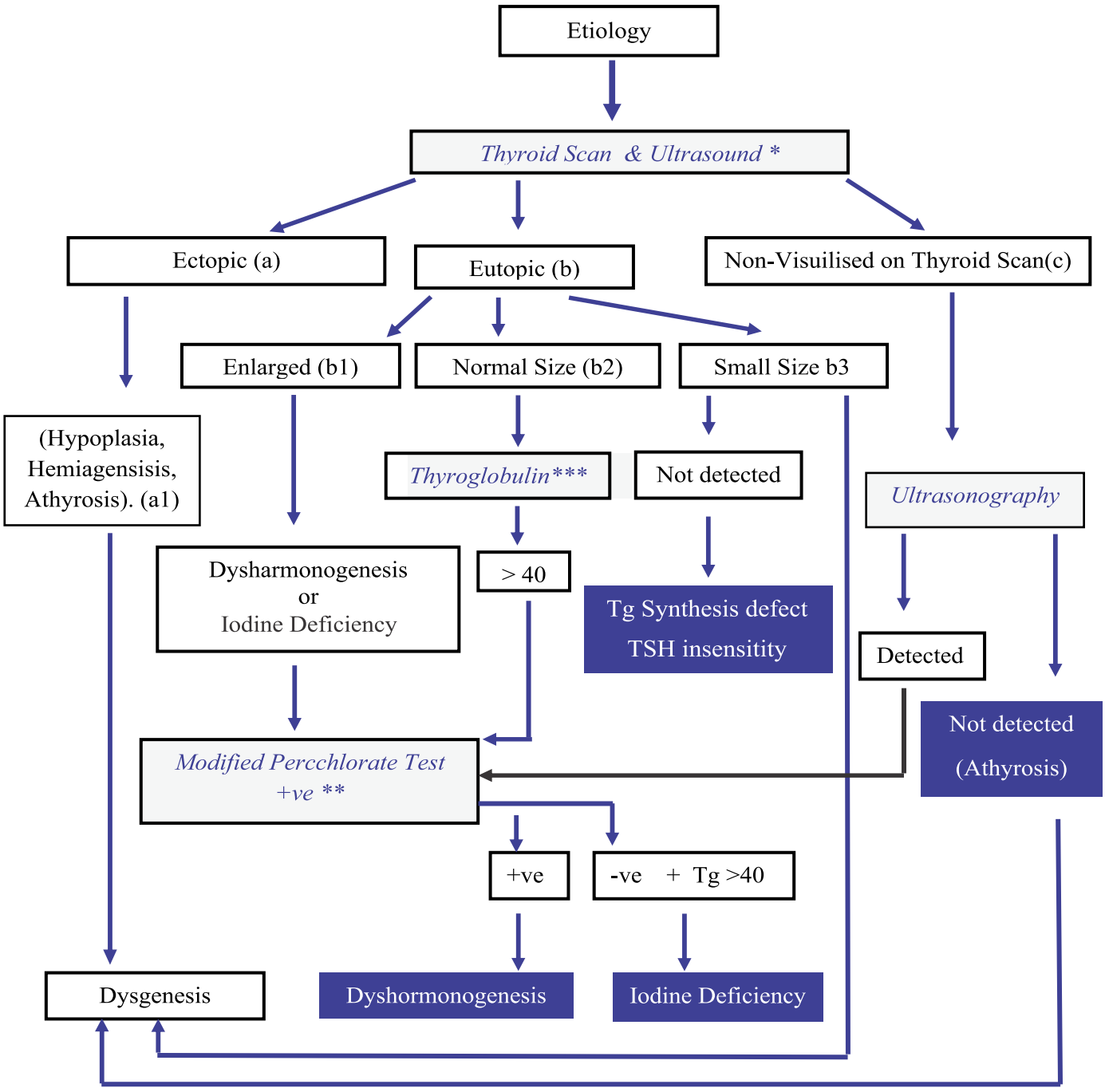

Figure 1: *Algorithm for etiological Diagnosis of Congenital Hypothyroidism.*

Footenote: * 1st step is **Thyroid Scan & Ultrasound** of Thyroid Gland which will reveal either of 3 findings (a) Ectopic (b) Eutopic (c) Non visualised.

- If **ECTOPIC**, (a) possibilities are, (a1) either Hypoplasia, Hemiagenesi or Athyrosis, 3 forms of DYSGENESIS.
- If **EUTOPIC**,(b) there are 3 posibilitiies, (b1)- Enlarged, (b2)-Normal or (b3)-Small . If Enlarged (b1) & **PERCHLORATE TEST (PT) is Positive diagnosis is DYSHORMONOGENESIS, if PT is negative & *** THYROGLOBULIN(Tg) Level is more than 40 Diagnosis will be IODINE DEFICIENCY. If Normal size (b2) Thyroglobin level more than 40 with positive PT diagnosis is DYSHORMONOGENESIS, while with negative PT diagnosis will be IODINE DEFICIENCY. Lastly if Small diagnosis will be Hypoplasia (DYSGENESIS).
- If **NON VISUILISED** (C) on Thyriod Scan but visuilised on Ultrasound, with positive PT, diagnosis will be DYSHORMONOGENESIS, with negative PT & Tg more than 40 diagnosisis will be IODINE DEFICIENCY.

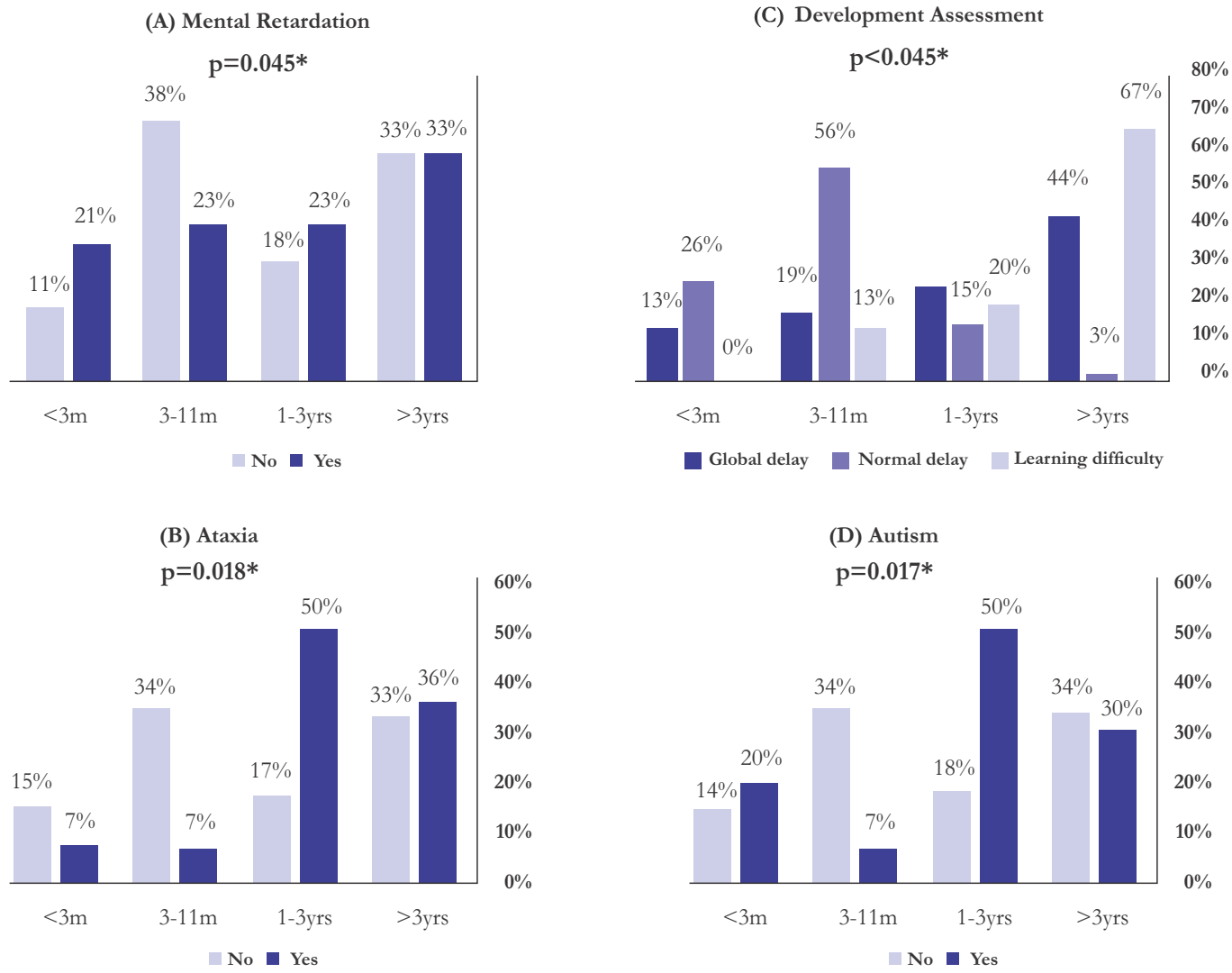

Figure 2: *Association of mental retardation (A), Ataxia (B), Developmental abnormality (C), and Autism (D). with Age at the time of diagnosis among cases of Congenital Hypothoroidism. Chi-square was used.*
**Significant level < 0.05*

physical development. The neonatal CH screening is recommended when a child is just 3 days old, whereas before discharge or within 7 days of birth, testing should be performed.[22] However, in developing countries like Pakistan, CH has not gained the proper medical attention, despite having significant incidence as 1:257 neonates found in a single centre study of newborn screening.[23] Early diagnosis of CH based on frequently occurring clinical features is still a burning dilemma and often linked to other diseases. In our study, more than half of the participants (66%, n=105/198) were diagnosed for CH at the age of 1-3 years of age, while only 14.6% (n=29/198) were diagnosed at the age <3 years. Furthermore, a significant association has been observed in our study between the age at diagnosis and development delay, autism, and ataxia. These results are consistent with the previous study conducted to observe delay in the diagnosis of CH, which had reported that the age at diagnosis of the majority of patients (42%,42/100) were 1-5 years and only 14% (14/100) patients were diagnosed before the age of three months.[19]

Furthermore, the common presentations of CH in our study were developmental delay, constipation, atypical facies, goiter, lethargy, patent anterior fontanelle, dry skin, learning difficulties, mental retardation, and short structure. However, goiter was seen in one-fourth of the study patients. According to another study conducted in Pakistan, developmental delay (66%), constipation (51%), lethargy (37%), short stature

(61%), coarse faces (53%), wide anterior fontanelle (46%), coarse skin (42%) were observed as common signs and symptoms, whereas goiter was reported in 7% cases.[19] In another study, the common clinical features of CH were constipation (11.6%), developmental delay (9.6%), and delayed development (9.1%).[8]

The delay in the diagnosis of CH can directly affect a child's physical growth and mental development. In our study, mental retardation was present in 8% patients (16/ 198), who were diagnosed < 3 months of age and these figures were reportedly more than three times higher (31.3%, 62/198) among those who were diagnosed after > 3 months. Similarly, a significant association has been seen between developmental delay and delay in the diagnosis of CH in our study. Global delay and learning difficulties were highest among those whose diagnosis was made after 3 years. Similar findings have been seen in a previous study where the developmental delay was most pronounced 100% (n=42) among children from 1-5 years.[18]

The etiology of CH includes Primary CH and Central CH. Among Primary CH, Dysgenesis (Athyreosis, Hypoplasia, Ectopic), Dyshormonogenesis, and Endemic Iodine deficiency included.[5,7] Previous studies had found that Dysgenesis was the most common Etiology (80 to 85%) of CH, with major share of Ectopic 85% followed by hypoplasia & Aplasia. Second most common etiological factor shown was Dyshormonogenesis (15 to 45%).[19,24,25,26]

On the other hand, Pakistan where approximately 70% of the population is still at risk of iodine-deficient disorders.[20] Iodine deficiency is still a considerable health issue in Pakistan even after decades of efforts to address the problem. About 40 percent of the population is still reluctant to use iodized salt, misconceptions like infertility prevail widely. The country's soil is already deficient in iodine because of flooding and erosion. According to UNICEF, the prevalence of iodine deficient disorders in the general population are still more than 80%.[21]

The above evidence verifies our study results. A high prevalence of dysgenesis (56.6%9, as etiological factor of CH, which is cmparable to previous studies, but hypoplasia (81%) rather than Ectopia (19%), was the major share of Dysgenesis. Similarly, iodine deficiency (26.6%) was the 2nd most common etiological factor rather than Dyshormono-genesis (14.1%), for the development of CH.

Thus, this study provides an insight into prevalence of CH etiology in iodine-deficient regions like Punjab. To the best of our knowledge, our comprehensive study highlights the gaps in early diagnosis of CH in tertiary care settings and emphasizes on the importance of clinical feature for the screening of CH in iodine-deficient endemic countries without National Neonatal Screening Program (NNSP).

The utilization of a validated structured questionnaire and wide canvas of etiological diagnosis, were the main strengths of our study.

Conclusion & Recommendations:

The primary health care physicians play a crucial role in the early evaluation of thyroid-related disorders among neonates and consequently timely referral to a pediatric health facility. The comprehensive knowledge of key clinical features of congenital hypothyroidism is essential to make early diagnosis and initiate prompt treatment of the disease, in the absence of National newborn screening programs in most developing countries. Moreover wide spread media compaign for Iodine Salt utilization is the need of time to avoid this crippling ailment.

Limitations of Study:

The data was collected through a non-probability consecutive sampling technique that limits the generalizability of the results of the study to a large population. As already diagnosed cases were enrolled so some parameters were assessed on recall base if record was not available.

Moreover, most of the study participants belonged to Punjabi ethnicity that further restricts the generalizability of the study results to other ethnic communities.

Results from a multicenter study can have generalized application.

Detailed thyroid autoantibodies screeing could not be done due to financilal reasons.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

Funding Source: None

References:

1. Venkateswarlu J, Hanmayyagari B, Nagender J, Neelaveni K, Sahay R, Jayanthy R. Evaluation of etiology, clinical profile and management outcomes in juvenile hypo and hyperthyroidism: A single centre experience. Thyroid Research and Practice. 2015 Jan 1;12(1):14.
2. Wang F, Jing P, Zhan P, Zhang H. Thyroid hormone in the pathogenesis of congenital intestinal dysganglionosis. Pediatric and developmental pathology: J of the Society for Pediatr pathology. 2020.
3. Diaz A, Lipman Diaz EG. Hypothyroidism. Pediatr Rev. 2014 Aug;35(8):336-47; quiz 348-9. doi: 10.1542/pir.35-8-336. Erratum in: Pediatr Rev. 2014 Oct;35(10):446. PMID: 25086165.
4. Mahmoud MM. Neglected case of congenital hypothyroidism in a 17-year-old female. International Journal of Case Reports and Images 2013;4(9):481–484.
5. Cherella CE, Wassner AJ. Congenital hypothy-roidism: insights into pathogenesis and treatment. Int J Pediatr Endocrinol. 2017:2017(1).
6. el-Desouki M, al-Jurayyan N, al-Nuaim A, et al. Thyroid scintigraphy and perchlorate discharge test in the diagnosis of congenital hypothyroidism. European Journal of Nuclear Medicine. 1995 Sep;22(9):1005-1008. DOI: 10.1007/bf00808411. Mäenpää J. Congenital hypothyroidism: aetiological and clinical aspects. Archives of disease in childhood. 1972 Dec 1;47 (256):914-23.
7. Chen CY, Lee KT, Lee CT, Lai WT, Huang YB. Epidemiology and clinical characteristics of congenital hypothyroidism in an Asian population: a nationwide population-based study. Journal of epidemiology. 2013 ;JE20120113:1-11.
8. Seth A, Aggarwal V, Maheshwari A. Hypothy-roidism in children beyond 5 y of age: delayed diagnosis of congenital hypothyroidism. The Indian Journal of Pediatrics. 2012 Jul 1;79(7):891-5.
9. Lakhani M, Khursheed M, Naqvi SH: Neonatal screening for Congenital Hypothyroid in Pakistan. J Pak Med Assoc 1989 Nov: 39(11):282-4
10. Yelluri SK. Incidence and etiology of thyroid disorders in children. Int J Contemp Pediatr. 2016;3(2):593-6.
11. Luca Chiovato, Flavia Magri, Allan Carle. Hypothyroidism in Context: Where We've Been and Where We're Going . Published online: September 4, 2019 ; 36:S47–S58.
12. Ashkan Habib, Alireza Shojazadeh, Mohadeseh Molayemat, Asadollah Habib, Marjan Jeddi, Rita Arabsolghar, etal. Revalence and predictive factors of transient and permanent congenital hypothyroidism in Fars province, Iran. BMC Pediatrics. 2021; 21:264.
13. Singh A, Purani C, Mandal A, Mehariya KM, Ranjan R. Prevalence of Thyroid Disorders in Children at a Tertiary Care Hospital in Western India. Journal of Clinical and Diagnostic Research. 2016;10(2):1-4.
14. Bezen, D., Dilek, E., Torun, N., and Tütüncüler, F. (2017). Etiological evaluation of primary congenital hypothyroidism cases. Turk pediatri arsivi, 52(2), 85–91. https://doi.org/10.5152/TurkPediatriArs.2017.3989
15. Rezaeian SH, Khazaei S, Hooshmand E, Esmailnasab N. Gender and Risk of Congenital Hypothyroidism: ASystematic Review and Meta-analysis. Int J Pediatr 2017; 5(12):6703-12. Doi: 10.22038/ijp.2017. 27473. 2368
16. Malik BA, Butt MA. Is delayed diagnosis of hypothyroidism still a problem in Faisalabad, Pakistan. Life. J Pak Med Assoc 2008; 10 (58):545-49.
17. Michael B. Zimmermann, Isabelle Aeberli, Maria Andersson, Vincent Assey, Jorge A. Jara Yorg, Pieter Jooste, etal. Thyroglobulin Is a Sensitive Measure of Both Deficient and Excess Iodine Intakes in Children and Indicates No Adverse Effects on Thyroid Function in the UIC Range of 100–299 mg/L: A UNICEF/ICCIDD Study Group Report. Published Online J Clin Endocrinol Metab. March 2013; 98(3):1271–1280.
18. DeMartino L, McMahon R, Caggana M, Tavakoli NP. Gender disparities in screening for congenital hypothyroidism using thyroxine as a primary screen. Europ J Endocrinol. 2018;179(3):161-167.
19. Diaz A, Elizabeth G, Diaz L, E. Hypothyroidism. Pediatrics in review. 2014; 35(8): 336–349. Doi: http://doi.org/10.1542/pir.35-8-336
20. Ghayur S, Siddiqui S, Alam MM, Shaukat A, Khan FA. Spectrum of iodine deficiency in school children of Rawalpindi. Pak Armed Forces Med J 2001; 51(1):27-32.
21. Shan Elahi, Nayab Batool Rizvi, Saeed Ahmad Nagra. Iodine deficiency in pregnant women of Lahore. JPMA 59:741; 2009.
22. Rose SR, Brown RS, American Academy of Pediatrics, American Thyroid Association. Update of newborn

screening and therapy for congenital hypothyroidism. Pediatrics. 2006 Jun 1;117(6):2290-303

23. Ahmad A, Wasim A, Hussain S, Saeed M, Ahmad BM, Rehman K. Congenital Hypothyroidism in Neonates of a Tertiary Care Hospital. Pak J Med Sci. 2017; 33(5):1269-1272. Doi: 10.12669/pjms.335.12986
24. Mohammed Al Jafari, Sachin Jose, Aisha Al Senani; Demographic Features and Etiology of Congenital Hypothyroidism at the National Diabetes and Endocrine Center in Oman from 2004 to 2016: Oman Medical Journal [2020], Vol. 35, No. 5: 171 .
25. Deniz Tanyeri, Ayşe Anık, Arzu Cengiz, Yasemin Durum Polat, Tolga Ünüvar, Ahmet Anık. Etiological Evaluation of Congenital Hypothyroidism in Cases Referred from the National Screening Program: J Pediatr Res 2021;8(1):1-6 DOI: 10.4274 / jpr.galenos. 2020.68736
26. Stephen H. LaFranchi. Approach to the Diagnosis and Treatment of Neonatal Hypothyroidism J Clin Endocrinol Metab, October 2011, 96(10):2959 –2967 .