Asia Pacific Journal of Pediatrics and Child Health

Volume 5, Oct - Dec 2022

Probiotics in Pediatrics: Quo Vadis?

Felizardo N. Gatcheco[1,2]

The explosion of research and knowledge on the role of the microbiome, specifically the gut microbiome, has brought forth a dazzling array of new ideas, concepts, innovations and more queries in the field of therapeutic and preventive medicine. The concept of the microbiome seems to explain the path...

Editorial Note HTML / PDF

Iron-Deficiency Anemia: Indonesia's Striving

Rini Sekartini [1], Nur Aisiyah Widjaja [2], Nurul Ratna Mutu Manikam [3], Juandy Jo [4,5], Ray Wagiu Basrowi [6], Charisma Dilantika [6]

Dear Professor Muhammad Ashraf Sultan, We are submitting our review, titled "Iron-Deficiency Anemia: Indonesia's Striving", for your consideration to publish in the Asia Pacific Journal of Pediatrics and Child Health. The nutritional-deficiency anemia, particularly iron-deficiency anemia...

Review Article HTML / PDF

Probiotic Use in Children with Functional Dyspepsia: A Systematic Review and Meta-Analysis

Jeanette I.Ch. Manoppo [1], Gregory Joey [1], Audrey M.I. Wahani [1]

Functional abdominal pain disorder is a functional gastrointestinal ailment, with symptoms including abdominal discomfort, bloating, regurgitation, and colic pain. A 2015 meta-analysis of 58 studies covering 196,472 children worldwide reported a pooled prevalence of functional abdominal pain disorde...

Meta Analysis HTML / PDF

The Impact of Singapore's COVID-19 Circuit Breaker Measures on Children with Developmental Delays and Their Families

Anitha Madayi [1], Yeleswarapu Sita Padmini [1], Chui Mae Wong [1]

COVID-19 has affected every aspect of life and the impact on different population groups has not been widely explored. Our aim was to evaluate the impact of the Covid-19 restrictions in Singapore ,on children with special needs and their families. This will help us to identify the key areas affect...

Research Article HTML / PDF

Monitoring Skeletal Muscle Growth in Children

Natte Raksadawan [1], Anawat Sermswan [1], Ukkrit Jansri [1]

Adequate skeletal muscle mass is essential for the health of both children and adults. Nutritional status of school children is monitored routinely using weight, height, and body mass index (BMI) z-score. We developed a practical paradigm to simultaneously monitor skeletal muscle growth, in addition...

Research Article HTML / PDF

Platelet count as predictive factor of renal involvement in Pediatric Henoch-Schonlein Purpura

Jessica Kireina [1], Reni Ghrahani [2], Sri Suryanti [3]

The aim of this study is to analyze the usefulness of increasing platelet count as a predictive factor of renal involvement in pediatric Henoch-Schonlein Purpura. Renal involvement is one of the most severe manifestation in HSP. Inflammation is a major indicator of severity in Henoch-Schonlein Purpu...

Research Article HTML / PDF

Review of COVID 19 data and mitigation efforts in India

Digant D Shastri [1], Dipsa D. Shastri[1]

From its first reported case on 30th January, 2020, India took 58 days to record 1,000 cases. It crossed 10,000 in another 16 days. From there to 1,00,000 was breached in 35 days. Since then the number of days to add an additional lakh cases has progressively gone down. India had a total of 571 cas...

Short Communication HTML / PDF

Caffey Disease mimicking as an osteomyelitis of ulna: A Case Report

Darshak Makadia [1], Sanjay Naik [1]

Caffey's disease or Infantile Cortical Hyperostosis (ICH) is a rare and mostly self limiting condition affecting young infants. 5 months old baby boy presented to our hospital with complains of fever, swelling in left forearm, irritability for 3 days. Initially he was treated as an osteomyelitis a...

Case Report HTML / PDF

Chronic Granulomatous Disease presenting first time in newborn period as neonatal sepsis due to staphylococcus aureus infection: A rare presentation.

Sudhir Mehta [1], Praveen Kumar [1]

Chronic Granulomatous Disease is characterized by defective intracellular bacterial and fungal killing in neutrophils and monocytes. It is caused by defects in NADPH oxidase, the enzyme complex responsible for generating the phagocyte respiratory burst. Catalase positive organisms can cause severe ...

Case Report HTML / PDF

Volume 3, Apr - Jun 2020

The COVID-19 Pandemic and Asia-Pacific Children

Aman B Pulungan[1]

Dear Editor in Chief, We hereby submit our editorial note on COVID-19 and Asia Pacific Children. Thank you. Aman B Pulungan amanpulungan@mac.com...

Editorial Note HTML / PDF

COVID-19 in children in Bangladesh: Situation analysis

Manzoor Hussain[1], Mohammad Abdullah Al Mamun[2]

Comparing to adults, so far the direct effects of COVID-19 on child and adolescent appears not significant. COVID-19 outbreak adversely affect different services among the children of Bangladesh. These include disruption to their healthcare, nutrition, protection, education, overall mental wellbeing...

Commentary HTML / PDF

How common is Hypothyroidism in Children with Epilepsy on Antiepileptic Drugs

Nur Rochmah[1], Muhammad Faizi[1], Nur Nailul[1], Prastiya Indra Gunawan[1]

Abstract Background:Epileptic children treated with oral antiepileptic drugs (AEDs) are at risk of hypothyroidism. However, there are still limited data about the influence of AEDs on thyroid function in children. Aims:To analyze thyroid function of epileptic children. Methods:A cross-sectional s...

Research Article HTML / PDF

OOSTENBRINK SCORE FOR DETECTING BACTERIAL MENINGITIS IN CHILDREN AT DR. MOEWARDI HOSPITAL

Arifatun Nisa[1], Fadhilah Tia Nur[1], Ganung Harsono[1]

Background: The clinical symptoms of bacterial meningitis are very broad, non-specific and there are no obvious symptoms. The diagnosis of the aetiology of meningitis in areas with limited resources is still constrained by several things. Several clinical predictors can help predict the incidence of...

Research Article HTML / PDF

ULTRASONOGRAPHIC FINDINGS IN CHILDREN WITH DENGUE FEVER ADMITTED TO A TERTIARY CARE HOSPITAL IN RAWALPINDI DURING 2019 OUTBREAK

Rai Muhammad Asghar[1], Rai Rijjal Ashraf[1], Mudassar Sharif[1], Muhammad Hussain[1], Abid Hussain[1]

Dengue fever is one of the most important emerging vector-borne viral diseases. There are four serotypes of dengue viruses, each of which is capable of causing self-limited dengue fever or even life-threatening dengue hemorrhagic fever and dengue shock syndrome. The aim of this study was to evaluate...

Research Article HTML / PDF

Prevalence and disease severity of multiple respiratory pathogens among children with severe lower respiratory tract infection

Lee Jeffrey Soon-Yit[1,2], Chua Tiing-Tiing[1], Ting Jakie[1,2], Wong See-Chang[2,3], Chieng Chae-Hee[2,3], Toh Teck-Hock[1,2,3]

A review of case records of children with severe lower respiratory tract infection (LRTI). We described the prevalence of children with severe LRTI who had multiple concurrent respiratory pathogens. The impact of multiple respiratory pathogens on the ventilator requirements, duration of ventilation ...

Research Article HTML / PDF

Dynamic of maternal vitamin 25(OH)D and 1,25(OH)2D level throughout pregnancy in small for gestational age infant: a cohort study of vitamin D impact on pregnancy in West Java- Indonesia

Setyorini Irianti[1], Raden Tina Dewi Judistiani[2], Sylvia Rachmayati[3], Jusuf Sulaeman Effendi[1], Budi Setiabudiawan[4]

ABSTRACT Different reports of Vitamin 25(OH)D and vitamin 1,25(OH)2D level in pregnancy showed different impact to pregnancy outcome. Those different results suggested a possible dynamic of vitamin D level throughout pregnancy which play role in pregnancy outcome. In this study, we describe differ...

Research Article HTML / PDF

GLUTARIC ACIDEMIA TYPE II IN A FILIPINO SCHOOL AGE CHILD

Leniza G. De Castro-Hamoy [1,2,3], Juan Carlo C. Viado [1], Novette Regina M. Lagunzad [1,3]

Glutaric Acidemia type II is a rare hereditary metabolic disorder involving fatty acid oxidation and amino acid metabolism. Symptoms can range from severe neonatal life-threatening events which may include physical abnormalities and acidosis to milder, late-onset presentations. The aims of this repo...

Research Article

How common is Hypothyroidism in Children with Epilepsy on Antiepileptic Drugs

Nur Rochmah[1], Muhammad Faizi[1], Nur Nailul[1], Prastiya Indra Gunawan[1]

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ABSTRACT:

Background: Epileptic children treated with oral antiepileptic drugs (AEDs) are at risk of hypothyroidism. However, there are still limited data about the influence of AEDs on thyroid function in children.

Aims: To analyze thyroid function of epileptic children.

Methods: A cross-sectional study was conducted during 2015 and 2020 at Dr. Soetomo Hospital Surabaya, Indonesia. Epileptic children treated with AEDs were included. Multiple AEDs were defined as more than one oral AEDs, which consisted of valproic acid, carbamazepine, phenytoin and phenobarbital. Hypothyroid was determined based on the decreased level of free thyroxine (fT4) and an increased level of thyroid stimulating hormone (TSH). Serum fT4 and TSH concentrations were measured in samples from epileptic children with single and multiple AEDs, and were compared using Chi-square and Mann-Whitney test.

Results: Forty-one children were included in the study, with twenty-seven (65.9%) epileptic children were treated with single AED. Thirteen children (31.7%) diagnosed with hypothyroidism, in which 5 children received multiple AEDs. Valproic acid was the most frequent AEDs given to the epileptic children (39 children). Mean level of fT4 and TSH were 1.32±0.25ng/dl and 4.5±4.03mIU/L. There were no significant differences of fT4 and TSH level between single and multiple AEDs (p=0.095, p=0.805). There was no significant difference in thyroid dysfunction between single and multiple AEDs (p=0.734).

Limitations: This is cross sectional study.

Conclusion: More than quarter epileptic children suffer from hypothyroidism.

Keywords: hypothyroid, epileptic children, antiepileptic drugs.

INTRODUCTION

Antiepileptic drugs (AEDs) therapy has been known to have multiple short- and long-term effects. The effects include endocrine disturbances, in particular, an alteration of the thyroid function.[1,2] Many AEDs may alter thyroid hormone homeostasis in biosynthesis, release, transport, metabolism and excretion of thyroid hormones.[3-5]

Several studies reported an increase in thyroid stimulating hormone (TSH) level, but in the vast majority of studies, decrease in thyroxine (T4) level, free thyroxine (fT4) level, triiodothyronine (T3) level, free triiodothyronine (fT3) level; and unchanged TSH levels had been reported in children using carbamazepine (CBZ) and phenobarbital (PB). Another study reported altered thyroid functions while using Valproic acid (VPA), however the results are controversial because there were normal or elevated serum levels of TSH.[4-6]

Single AED has been promoted as an ideal therapy for epilepsy because of its minimal side effects, absence of drug interactions, better compliance, lower cost and improvement of seizure control compared to multiple AEDs.[7] A previous study showed that epileptic patients receiving multiple AEDs had an increase mean level of TSH, resulting symptoms and signs of hypothyroidism, compared to those receiving single AED.[8,9]

Hypothyroidism in children can have harmful effects on the growth, school achievement and pubertal development.[10,11] Pediatricians should be alerted about conditions that may be associated to the children receiving AED. However, there are still limited data about the influence of AEDs on thyroid function in children. Thus, we aimed to analyze thyroid function of epileptic children.

METHODS

This comparative cross-sectional study was conducted during 2015 and 2020 at pediatric neurology outpatient clinic Dr. Soetomo Hospital, Surabaya, Indonesia. Patients who fulfilled inclusion criteria were included in the study.

Inclusion criteria

Children aged less than 18 years who had been diagnosed with epilepsy by clinical examination and EEG and received AEDs for more than 3 months were included.

Exclusion criteria

(i) Any neurological or psychiatric disorder other than epilepsy, thyroid disease, and others chronic diseases;
(ii) Long term medication that could affect thyroid function;
(iii) Thyroid or endocrine dysfunction before the start of treatment

Informed consent was taken from parents before participation.

Anthropometric measurements of age, gender, and weight were recorded. Serum TSH level and serum fT4 level were collected. Hypothyroidism was determined based on the decreased level of fT4 and an increased level of TSH and assessed according to the normal level of the thyroid function test based on the age of the subjects. Multiple AEDs was defined as more than one oral AEDs. In this study, the AEDs were Valproic acid, Carbamazepine, Phenytoin and Phenobarbital.

Calculations were done with the statistical package SPSS for windows, version 12.0 (SPSS Inc., Chicago, IL, USA) through which, descriptive statistics were calculated. Descriptive statistics i.e. mean, standard deviation (SD), median, range and frequency were calculated. The statistical difference of the variable was analyzed by Chi-square and Mann Whitney test. Values of $p<0.05$ (two-tailed) were considered statistically significant.

RESULTS

A total of 41 children with epilepsy on AEDs were screened for eligibility, with 23 (56.1%) subjects were male. Median age of the subjects was 37 (5-168) months old with the median weight of 12 (4.7-55.5) kg. There were 5 (12.2%) children who received AEDs for less than 6 months and 36 (87.8%) children receiving AEDs for more than 6 months. The clinical characteristics of the studied subjects are shown in Table 1.

Median fT4 and TSH level of the children receiving AEDs for less than 6 months was 1.32 ng/dL and 2.48 mIU/L, while those receiving AEDs for more than 6 months had median fT4 and TSH level of 1.30 ng/dL and 3.21 mIU/L. Children on AEDs for more than 6 months showed high incidence of hypothyroidism (13/36) compared to those receiving AEDs for less than 6 months (0/5), but there was no significant difference between groups ($p=0.160$).

There were 61% children receiving valproic acid and 4.9% receiving phenytoin alone. Combination valproic acid and phenytoin; valproic acid and phenobarbital; valproic acid and phenobarbital and phenytoin; valproic acid and carbamazepine were observed in 22%; 4.9%;4.9% and 2.4% patients respectively.

Mean fT4 level of all the subjects was 1.32±0.25 ng/dL, while the mean TSH level was 4.5±4.03 mIU/L. The normal range for children 2-7 years old for FT4 was 1.0-2.1 while TSH 0.7-5.7. The normal range for 8-20 years old for FT4 was 0.8-1.9 while TSH was 0.7-5.7.[12] The comparisons of the mean levels of the thyroid function test between single and multiple AEDs are shown in Table 2. There were no significant differences in fT4 and TSH levels between groups ($p=0.095$, $p=0.805$).

Thirteen (31.7%) epileptic children were diagnosed with hypothyroidism. Hypothyroidism was frequently seen in patients on multiple AEDs compared to single AED (Table 3). There was no significant difference in thyroid dysfunction between single and multiple AEDs ($p=0.734$). From 39 children receiving valproic acid, there were 12 (30.8%) children diagnosed with hypothyroidism. Among 12 children receiving valproic acid, 7 treated with valproic acid alone and 3 valproic acid and phenytoin, 1 valproic acid, phenytoin and phenobarbital, while 1 valproic acid, phenytoin and carbamazepine.

Table 1. Demographic and clinical features of the studied patients.

Variable	N = 41
Gender (%)	
Male	23 (56.1%)
Female	18 (43.9%)
Age, month old	37 (5-168)
Weight, kg	12 (4.7-55.5)
Duration of therapy, months	17 (5-102)
AED	
Single therapy	27 (65.9%)
Multiple therapy	14 (34.1%)
Antiepileptic drugs utilized	
CBZ	1 (2.4%)
VPA	39 (95.1%)
Phenytoin	14 (34.1%)
Phenobarbital	4 (9.7%)
fT4 level, ng/dl	1.32 ± 0.25
TSH level, mIU/L	4.5 ± 4.03

* Data are expressed as n (%) or median (minimum-maximum) or mean ± SD.

Table 2. Comparison of thyroid function test between single and multiple AEDs.

Variable	Single AEDs	Multiple AEDs	*P* Value
fT4 (ng/dl), mean ± SD	1.36 ± 0.26	1.22± 0.22	0.095
TSH (mIU/L), mean ± SD	4.58 ± 4.23	4.37± 3.75	0.805

Table 3. Comparison of thyroid dysfunction between single and multiple AEDs.

AEDs	Hypothyroid		*P* Value
	Yes	No	
Single therapy	8 (29.6%)	19 (70.4%)	0.734
Multiple therapy	5 (35.7%)	9 (64.3%)	

DISCUSSION

In our study, hypothyroid was reported in 13 (31.7%) children receiving AEDs. The disturbances in thyroid hormone homeostasis associated with AEDs were reported for the first time in 1961.[13] Several studies found that epileptic patients receiving AEDs might precipitate hypothyroidism.[9,14,15] Another studies reported abnormal thyroid hormonal levels with enzyme-inducing AEDs (CBZ, phenytoin, PB) and normal thyroid hormonal levels with non-enzyme-inducing AEDs (VPA).[1,2,13]

Valproic acid and carbamazepine therapy are known to affect the thyroid hormone levels by different mechanism. Carbamazepine induces the P-450 enzyme system and its consequent are the increase in the metabolism of thyroid hormones, meanwhile in VPA, inhibition of somatostatin, a potential inhibitor of TSH secretion, via an γ-aminobutyric acidergic effect has been proposed as a basic mechanism.[5,16]

Our study showed that TSH levels in children receiving AEDs (CBZ, VPA, phenytoin, PB) were increased. This result is in accordance with several studies who found that CBZ and phenytoin increased TSH level.[6,14,15] This result is in partial agreement with a previous study who found that CBZ increased TSH level, but VPA had variable effects on TSH level.[17] On the other hand, a previous study reported thyroid dysfunction in men taking AEDs (CBZ and VPA) a decrease in T4 level, but there is no alteration in TSH and T3 levels.[9] Yılmaz et al.[18] reported hypothyroid in 13.9% with CBZ. Another study by Isojarviet al.[9] reported reduced levels

of T4 in 53.3% and fT4 in 28.9% with CBZ. Eirís-Puñalet al.[19] reported increased levels of TSH in 8.2% (versus 3.6% for controls). Valproic acid was used in 39 patients (95.1%) of this study and there were 30.8% with hypothyroidism. This result was in agreement with Mikati et al.[20] that showed from 43 epileptic patients with VPA, 25.2% of them had high TSH serum level.

We found that the number of epileptic children on AEDs who had hypothyroidism increased in multiple AEDs (5 patients out of 14) compared to those receiving single AED (8 patients out of 27). A study showed reduced levels of fT4 in 50-100% of patients on multiple AEDs with CBZ and VPA.[9] Another study showed an increase in the thyroid hormones (including TSH) concentration in epileptic patients receiving AED and these changes were significantly more common in patients undergoing anticonvulsant multiple therapy.[8]

In this study, children on long-term therapy showed high incidence of hypothyroid (13/36), while those receiving short-term therapy showed no evidence of hypothyroid. A study which assessed the thyroid status of patients receiving long-term anticonvulsant therapy found that the mean serum TSH level was slightly increased, thus resulting in the elevation of the clinical score of subclinical hypothyroidism.[21]

Despite the strength of this study, it has some limitations: 1) the recruitment of the study group from a tertiary care center with more severe cases and this explains a high percentage of thyroid hormonal abnormalities. However, it should be kept in mind that hypothyroid is a relatively common condition with the incidence between 3-7% in the general population. Hence probably, such frequency rates for hypothyroid might be increased among the patients with epilepsy, which is also common, and 2) because of its cross-sectional study, it was not possible to know temporal relationship between thyroid dysfunction and AEDs therapy. However, such limitations could only be overcome through a longitudinal and multi-center study design.

CONCLUSION

Hypothyroidism is more frequent, found in more than quarter epileptic children. It might be worthy to measure serum fT4, TSH regularly, especially those on multiple AEDs, regardless of the type of AEDs to avoid development of overt hypothyroidism. This data indicates the importance of monitoring thyroid function in patients with epilepsy and on treatment with AEDs. This data also may have implications suggesting prevention strategies.

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