Association of first-trimester screening biomarkers and the prevalence of cerebral palsy and other neurodevelopmental conditions: A systematic review

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ABSTRACT

Objective: To determine the association between first-trimester screening biomarkers and the prevalence of cerebral palsy and other neurodevelopmental disorders.

Methods: This study was registered at PROSPERO (CRD42021268911). A systematic literature search was performed using PubMed, Cochrane, CINAHL databases, and Google Scholar between May 2021 and January 2022. Observational studies included pregnant participants with recorded maternal serum markers (hCG and PAPP-A) and outcome measures on the prevalence of cerebral palsy, or other neurodevelopmental conditions.

Results: The review identified 248 non-duplicate studies, with only five studies having met the inclusion criteria. Based on this review, combined low levels of β-hCG were correlated with an increased risk of the development of cerebral palsy [OR] of 2.63 (95%CI 1.07, 6.46, p=0.04), and autism spectrum disorder [OR] of 1.16 (95% CI: 1.02 to 1.32, p<0.05) in infants. PAPP-A levels were also correlated with cerebral palsy [OR] of 1.81 (95%CI: 1.22-2.64, p<0.01). There are non-significant associations between β-hCG and CP and first-trimester screening markers and risk of neurodevelopmental conditions [OR] of 0.48 (95% CI: 0.3-0.8, p=0.05).

Conclusion: There are only limited studies that showed plausible associations between hCG and autism; and PAPP-A alone and combined hCG and PAPP-A with cerebral palsy. More studies are needed to search for potential mechanisms behind abnormal FTS markers and the CNS development of infants with neurodevelopmental conditions.

INTRODUCTION

Neurodevelopmental disorders (NDDs) are conditions caused by impaired brain development characterized with problems in behavior, cognition (memory or learning), or motor skills (WHO, 2011; and Mullin et al., 2013). These include

intellectual disability, communication disorders, attention deficit hyperactivity disorder (ADHD), learning deficits, autism spectrum disorder (WHO, 2011; and Mullin et al., 2013), and cerebral palsy (WHO, 2011).

NDDs were caused by different environmental and genetic factors that hindered brain development (Parenti et al., 2020, Irie et al., 2022). The review by Irie et al. (2022) highlighted mutations in the ASD-associated genes (i.e. FOXP2, CLOCK, and ELAVL2) which have roles in brain development. The review by Parenti et al. (2020) also discussed gene mutations during neural development that can result in problems in protein synthesis, transcriptional and epigenetic dysregulation, and disruption in synaptic signaling as possible causes of NDDs.

Since neurodevelopmental disorders are identified based on clinical presentation, there are challenges in finding the appropriate diagnosis and treatment for the patients (Mullin et al., 2013). For cerebral palsy alone, a delayed diagnosis can occur as late as five years in underdeveloped countries which is beyond the optimum timeframe for interventions that utilize the neuroplasticity of the developing brain (te Velde et al., 2019). This is evident in the Philippines as presented in the study of Hebreo et al (2017) where only 35 participants out of 125 (29%) had confirmed diagnosis of cerebral palsy during 2007-2009 in the Philippine General Hospital.

A possible solution to the problem is to find potential screening markers that can detect risks of developing NDDs in utero. The first-trimester screening markers have already been used as a non-invasive blood test during the 10th to 14th week of gestation to detect problems with pregnancy (Shiefa et al., 2012). Combined abnormal levels of screening markers - hCG and PAPP-A, in combination with maternal age and nuchal translucency can also yield an 83% detection rate of Down syndrome, with 5% false positive results (Chitayat et al., 2011). Low PAPP-A levels have also been associated with adverse pregnancy outcomes (e.g. preeclampsia, fetal growth restriction, and placental problems) (Gomes et al., 2017). It has yet to be elucidated if first-trimester screening markers are associated with neurodevelopmental disorders, especially cerebral palsy.

The primary objective of the review is to determine the association between first-trimester screening biomarkers and the prevalence of cerebral palsy and other neurodevelopmental disorders. This study can help explore potential molecular mechanisms behind abnormal values of first-trimester screening biomarkers and the CNS development of infants with neurodevelopmental conditions.

METHODOLOGY

This study followed the PRISMA statement for systematic review and meta-analysis (Liberati et al., 2009). This study was also registered at PROSPERO under the identification code CRD42021268911. No amendments were made to the protocol which can be accessed at https://www.crd.york.ac.uk/PROSPERO.

Database Search
A systematic literature search was performed in PubMed, Cochrane, CINAHL databases on May 13, 2021 while an updated search on google scholar was performed in January 2022. The search terms were based on the following PICO framework: population ("pregnant women" or "pregnancy"), indicator/diagnostic test ("first trimester screening biomarkers", "PAPP-A", "pregnancy-associated plasma protein A", "hCG", or "Human chorionic gonadotropin"), outcome ("cerebral palsy",

"neurodevelopment delay", or "brain malformation") (See Appendix I for data search terms and strategies).

Study Selection
The studies included in the review met the following inclusion criteria: (1) pregnant women who were 18 years old and above, (2) studies with maternal serum markers: hCg and PAPP-A, (3) outcome measure of the study should be the prevalence of CP, or other neurodevelopmental conditions such as autism, ADHD, or intellectual disabilities, and (4) type of study should be observational cohort, cross-sectional studies, or case-control studies.

The studies were excluded if they met any of the following exclusion criteria: (1) studies involving medical intervention during the pregnancy, (2) studies without available full text, (3) studies that are not translated in English, or (4) outcome measures focused on the prevalence of aneuploidy or genetic disorders (See Appendix II for publications or studies excluded after full-text screening).

All studies that qualified during title screening were placed by (1) researcher on an MS Excel sheet. The abstract and full-text screening were performed manually and were also encoded by the same researcher in the MS Excel sheet file. The results of the study selection were verified by an independent researcher of the study.

Data Extraction and Risk of Bias Assessment
The studies were extracted by (2) independent researchers who decided which studies to be included based on sets of inclusion and exclusion criteria. The studies selected underwent risk of bias assessment by 2 independent assessors using the Newcastle-Ottawa scale (Wells et al., 2009). Disagreements between the assessments were discussed and resolved by the 2 independent assessors. If there is missing data in a study, the researchers will contact the authors of the study to request the missing information. Studies will not be included in data analysis if the data is not available despite being contacted by the researcher.

Data Analysis
A qualitative synthesis was performed which included the PRISMA flow chart, summary tables of studies, and a narrative synthesis of the results explaining the characteristics of the studies included and the general results of the study for each neurodevelopment condition.

If there are at least 2 similar studies reporting for a neurodevelopment condition, and the studies are relatively of good quality based on risk of bias assessment, a random effects model meta-analysis can be performed by pooling the odds ratio of hCG and PAPP-A with NDDs, and presenting the forest plots of the serum markers using the RevMan 5.1 (Review Manager, 2011).

RESULTS

Studies Included
Upon review, there were 248 non-duplicate studies from the 3 databases and 1 search engine utilized (PUBMED, COCHRANE, CINAHL, and Google Scholar) from May 2021 to January 2022. 238 studies were removed after the title and abstract screening due to the following: 213 studies with wrong participants (non-pregnant women or pregnant women receiving intervention), 9 studies with no outcome measures of interest, 9 studies wrong study type (animal studies) and 7 studies with no first-trimester screening markers. Out of 10 studies included, only 9 studies were retrieved for full-text screening. Only 5 studies met the inclusion criteria and were included in the

analysis based on the inclusion and exclusion criteria by the reviewer (See Figure 1). The results of screening, data extraction, and risk of bias assessment can be accessed upon request from the author (jrlentejas@up.edu.ph).
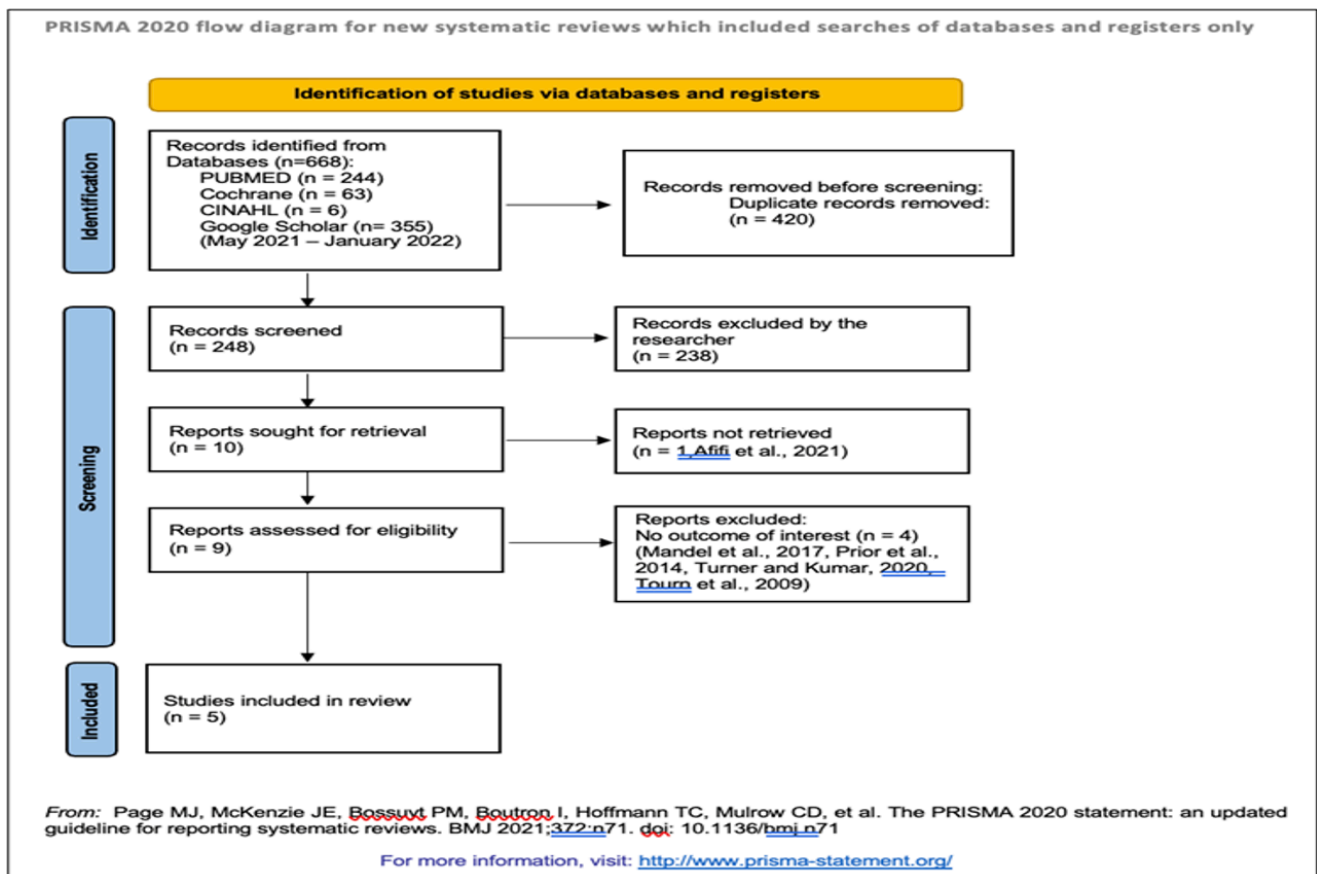

Figure 1: Prisma Flowchart

Legend: PRISMA - Preferred reporting items for systematic reviews and meta-analyses. Narrative: The review yielded a total of 668 studies, with 244 records from PUBMED, 63 from Cochrane, 6 from CINAHL, and 355 from google scholar. There are 248 unique records for the title and abstract screening after removing the duplicate studies. Out of 248 records, 238 studies were removed after title and abstract screening resulting to 10 studies to be included in full text screening. Only 9 studies were retrieved for full text screening, with 4 studies excluded due to: (2) studies including genetic disorders, and (2) other studies with no outcome of measure of interest. Only 5 studies were included in the review: Ayras et al., 2019; Eskild et al.,2018; Peris et al., 2021; Windham et al., 2016; Tsompanidis et al., 2021.

Characteristics of the Studies Included
Of the 5 studies included, 4 were case-control studies, and 1 was a cohort study. The cohort study by Ayras et al. (2019) reported on neurodevelopmental impairment. Two case-control studies reported on the incidence of cerebral palsy (Eskild et al.,2018; Peris et al., 2021) and the other two studies (Windham et al., 2016; Tsompanidis et al., 2021) included participants with autism spectrum disorder. The study characteristics were summarized in Table 1.

Risk of Bias Assessment
Based on the Newcastle-Ottawa scale (NOS) for the case-control studies, out of 4 studies, 3 had a low risk of bias (Ayras et al., 2019; Eskild et al., 2018; and Peris et al., 2021), while only one study (Windham et al., 2016) had a high risk of bias due to lack of information regarding participant selection. The cohort study (Tsompanidis et al., 2021) also had a low risk of bias based on the Newcastle-Ottawa scale (NOS) for cohort studies. See Table 2 for results of the risk of bias assessments.

Neurodevelopmental Conditions
The study by Ayras et al. (2019) showed a non-significant association between high-risk mothers with abnormal first-trimester screening values and risk of developing adverse outcomes (including neurodevelopmental conditions) compared to the control group with (OR 2.1, 95% CI 1.0, 4.5,p = 0.05). This was adjusted for the mother's age, parity, and smoking habits. In terms of individual first-trimester screening markers, only PAPP-A was considered significant with a decreased risk of an adverse outcome when there was a higher PAPP-A level (OR 0.48, 95% CI 0.3, 0.8). See Table 3 for a summary of the findings.

Cerebral Palsy (CP)
There was no significant association between mothers with low levels of hCG in both the first and second trimester and increased risk for having a child with cerebral palsy with (OR) 2.75 (95%CI 0.84, 9.04, p<0.10) (Eskild et al., 2018). This was also supported by the study of Peris et al. (2021) which also found a similar pattern of increased risk for having a child with CP with (OR) 1.38 (95%CI 0.88, 2.08, p=0.12), although not significant. In addition, Peris et al. (2021) also noted an increased risk of having a child with CP with both low PAPP-A levels and combined low PAPP-A and low hCG with (OR) of 1.81 (95%CI 1.22, 2.64, p<0.01), and (OR) 2.63 (95%CI 1.07, 6.46, p=0.04), respectively. In the study of Eskild et al. (2018), the OR score was adjusted for age of gestation during sampling, age of the mother, and parity. The OR score for the study of Peris et al. (2021) was also adjusted for age of gestation at testing and maternal weight. See Table 3 for a summary of the findings.

Autism Spectrum Disorder (ASD)
The study of Windham et al. (2016) showed that both extremely low levels of hCG with (OR) of 1.16 (95% CI 1.02, 1.32), and

extremely high levels of hCG with (OR) 1.19 (95%CI 1.05, 1.36) of pregnant mothers were significantly correlated with children having an ASD diagnosis (p<0.05). This is also supported by the study of Tsompanidis et al. (2021) that found an association between low hCG levels and autistic traits measured by the Q-CHAT questionnaire (Beta=2.95, SE=1.07, p=0.007). The OR for Windham et al11 was adjusted to the mother's age, race, and sex of the child. The multiple regression performed in the study of Tsompanidis et al. (2021) was also adjusted in terms of the maternal age, maternal autism spectrum quotient (ASQ), PCOS diagnosis, and the infant's birth weight and age. See Table 3 for a summary of these findings.

Table 1: Characteristic of studies and their participants included in the review

Study	Type of Study	Sample Size (n=)	Participant Characteristics	Condition	Assessment/Markers
Peris et al., 2020	Retrospective Case Control	1376 (435 CP cases; 941 non CP controls)	singleton births in Victoria between 2001 and 2017 with no known post-neonatal cause of CP and no known outcome of trisomy 21, with children born with CP based on Victorian Cerebral Palsy Register (cases), and matched healthy children (controls)	Cerebral Palsy	first-trimester screening (cFTS) biomarkers
Eskild et al., 2018	Case Control	127 (CP Case=30; Control=90)	singleton pregnancies in Norway during 1992–1994 from Toxoplasmosis Study, with children diagnosed with CP before 5 years of age based on The Norwegian Registry of Cerebral Palsy (cases), and no CP diagnosis (controls)	Cerebral Palsy	1st, 2nd, and 3rd trimester (β-hCG)
Ayras et al., 2019	Case Control	483 (161 Cases, 322 Control)	singleton births who visited the Fetal Medicine Center of Helsinki University Hospital during 2009−2012, with a high risk (≥1:50) based on FTS for trisomy 21 and normal karyotype (cases), and with low risk of (< 1:300) for trisomy 21 (controls)	syndromes, genetic disorders, structural defects, or neurodevelopmental impairment	First trimester screening tests (NT, PAPP-A, β-hCG)
Windham et al., 2016	Case Control	602,689 (2,586 Cases, 600,103 Control)	pregnant women whose blood was drawn during the second trimester at 15–20 weeks gestation and who gave birth in either 1996 or 2002 were obtained from the Genetics Disease Screening Program (GDSP) of the California Department of Public Health.	Autism Spectrum Disorder	Second trimester screening (β-hCG)
Tsompaminidis et al., 2021	Cohort	219	singleton pregnancy, during or immediately before their routine 20-week ultrasound scan between 2016 and 2018 at the Rosie Hospital, Cambridge University Hospitals NHS Foundation Trust, mothers should not have taken alcohol, recreational drug, or smoking during pregnancy, and no IUGR or LGA	Autism Spectrum Disorder	Late first trimester screening (β-hCG and PAPP-A)

Legend: CP – cerebral palsy, FTS – first trimester screening, IUGR - intrauterine growth retardation, hCG - Human chorionic gonadotropin, LGA – large for gestational age, NT – nuchal translucency, and PAPP-A - Pregnancy-associated plasma protein A.

Table 2: Results of risk of bias assessment (Newcastle-Ottawa scale for case-control and cohort studies)

STUDIES	SELECTION	COMPARABILITY	EXPOSURE
CASE CONTROL			
Ayras et al., 2019	☆☆☆☆	☆	☆☆☆
Eskid et al., 2018	☆☆☆	☆☆	☆☆
Peris et al., 2020	☆☆☆	☆	☆☆☆
Windham et al., 2016	-	☆☆	☆☆
COHORT			
Tsompaminidis et al., 2021	☆☆☆☆	☆☆	☆☆

Legend: For selection (max of 4 stars), for comparability (max of 2 stars), and for exposure (max of 3 stars) based on Newcastle-Ottawa scale.

Table 3: Summary of findings

STUDY	CONDITION	SCREENING MARKERS	ODDS RATIO/CORRELATION COEFFICIENT	P-value
Eskild et al., 2018	Cerebral Palsy	Low hCG concentration in 1st and 2nd Trimester (50 439-10 368 IU/L)	[OR] 2.75 (0.84-9.04), adjustment for mother's age and parity	P<0.10***
Peris et al., 2020	Cerebral Palsy	Extreme low β-hCG (<0.40 MoM)	6.4% cases vs 4.8% controls; [OR] 1.38 (0.88-2.08)	p=0.12
		Extreme low PAPP-A (<0.42 MoM)	8.3% cases vs 4.7% controls; [OR] 1.81 (95%CI 1.22-2.64)	P<0.01***
		Extreme low β-hCG and PAPP-A	1.4% cases vs. 0.6% controls, [OR] 2.63 (1.07-6.46)	p=0.04***
Windham et al., 2016	Autism Spectrum Disorder	Extreme low hCG (<10th percentile)	5.0 per 1000 screened births; [OR] 1.16 (1.02-1.32)	P<0.05***
		Extreme high hCG (>90th percentile)	4.8 per 1000 screened births; [OR] 1.19 (1.05-1.36)	P<0.05***
Tsompanidis et al., 2021	Autism Spectrum Disorder (Q-CHAT)	hCG	(Beta=2.95, SE=1.07; Semi-partial correlation coefficient=0.24)	p=0.007*** Significant correlation
		PAPP-A	(Beta=1.69, SE=1.45; Semi-partial correlation coefficient=0.11)	p=0.245 Not significant correlation
Ayras et al., 2019	Adverse Outcome (including neurodevelopmental condition)	Low hCG levels	Not significant	p>0.05
		Low PAPP-A levels	[OR] 0.48 (95% CI: 0.3-0.8)	p=0.05***

Legend: *** - *p-value is significant in the study*

DISCUSSION

Early diagnosis for neurodevelopmental conditions is difficult due to the lack of biomarkers that can be used for screening, like in the case of cerebral palsy (McIntyre et al., 2011), and autism (Bello-Mojeed et al., 2017). This often leads to delayed diagnosis and management of the affected child. According to the study by Hus & Segal (2021), early diagnosis, and management can help in improving functional outcomes, especially for children with ASD.

Currently, we have existing prenatal screening tests which can possibly assist in identifying the need for further assessment leading to proper management and counseling. The first-trimester screening markers can help detect pregnancies at risk for fetal aneuploidy (Driscoll and Gross, 2008), other fetal

anatomical abnormalities, and obstetric complications (D'Alton and Cleary-Goldman, 2005). With this, the review explored the association between first-trimester screening markers and children with neurodevelopmental conditions.

Based on this review, there is a significant association between abnormal levels of β-hCG and increased risk of development of autism and autistic traits (Windham et al., 2016, Tsompanidis et al., 2021). Although there are uncertain associations between low levels of β-hCG and increased risk of development of CP (Eskild et al., 2018, Paris et al., 2020), the association to increased risk of CP improved with both combined low levels of β-hCG and PAPP-A (Paris et al., 2020). In the normal physiology of pregnancy, hCG is an important hormone to preserve the embryo by maintaining progesterone production of the corpus luteum (d'Hauterive et al., 2022). When hCG levels are abnormal, placental development could be affected resulting in fetal growth restriction (Peris et al., 2021), and maternal complications such as preterm delivery and preeclampsia (Simeon et al., 2021). All these may result in poor fetal outcomes that include neurodevelopmental conditions. The latter is possibly explained by the hypothesized role of hCG in hemochorial placentas for the development of our advanced human brain (Theofanakis et al., 2017). Moreover, another study by Miranda and Sousa (2018) found that the relationship between hCG and its role in thyroid hormone production, with low levels of the latter hormone during the first-trimester can cause neurodevelopmental problems.

PAPP-A has also been correlated with CP and the possible development of adverse outcomes that include neurodevelopmental conditions. Like hCG, this biomarker has been hypothesized to be important for placental growth and development (Kirkegaard et al., 2010). It has also been used clinically due to its association with preterm birth and small-for-gestational age (SGA) babies (Livrinova et al., 2018). The study of Livrinova et al. (2018) also found low levels of PAPP-A associated with fetal hypoxia and high blood pressure during pregnancy which can affect neurodevelopment.

The abovementioned studies introduce the plausible physiological mechanism of having abnormal first-trimester screening markers and poor CNS development of infants with neuro-developmental conditions. However, the correlation did not take into consideration the other factors in perinatal and antenatal care which can affect the chances of developing neurodevelopmental conditions. According to a study by Wang et al. (2017), other perinatal and postnatal factors can increase the risk of autism e.g. type of delivery, fetal distress, and low birth weight. This is also supported by the cohort study by Joud et al. (2020) which discussed perinatal factors (e.g. mode of delivery and admission to neonatal care), and antenatal factors (e.g. small-for-gestational age, malformation). More studies are still needed to further identify causal relationships between FTS and infants at-risk of specific neurodevelopmental problems. Also, further research on the association of these markers to other neurodevelopmental conditions not included in this paper may present a better understanding of the relationships between the clinical spectra of these diseases.

In conclusion, only limited studies have shown plausible associations between hCG and autism, and PAPP-A alone or combined screening markers (hCG and PAPP-A) with cerebral palsy. This may be due to poor placentation and multiple hormonal imbalances in utero which ultimately affect neurodevelopment. Our review is also in support of other studies linking these biomarkers to other complications like SGA, and other pregnancy complications (e.g. preeclampsia, and preterm birth).

This review has limitations in terms of publication bias. Further literature review of unpublished studies is needed to improve the reliability of the results of the study. Another limitation of the review is the use of the broad term "neurodevelopmental condition" as a search strategy. Identification and inclusion of specific conditions should be considered to include other relevant studies for the review.

DISCLOSURE STATEMENT

The researchers have no financial conflicts of interest to disclose.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

JPRL – Conceptualization, Methodology, Literature search, Data extraction, Risk of bias assessment, Data Analysis, Writing (initial draft and editing); CLV - Conceptualization, Literature search, Data extraction, Risk of bias assessment, Data Analysis, Writing (initial draft and editing).

CONFLICT OF INTEREST

The researchers of this review do not have any conflict of interest.

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