

## Is there a Side-Effect by Using Medical Ultrasound Regarding Autism and Other Fetal Pathologies?

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### Abstract

**Introduction:** Random and prospective study was performed to determine the effect of ultrasound scanning as one of the contributing factors in autism at early gestational scanning among seven ethnicity groups.

**Aim of the Study:** The aim of this study was to see if ultrasound scanning may or may not cause Autism or other pathologies.

**Methodology:** During March 1991 - March 2008, 5800 women were sonographically scanned in multi centers and hospitals in Canada, Saudi Arabia, and Brunei Darussalam. The ultrasound scanning was carried on for routine obstetrical purposes and other reasons such as to check for viability, ectopic pregnancy, cysts, free fluid, Placental abruption and unsure of date. The autism spectrum disorder cases were documented in 4- and 5-years child age and the results were tabulated accordingly.

**Results:** From the 5800 patients the author managed to get feedback from 4200 patients. Total autism children reported were 23 children, 12 which were diagnosed with other anomalies.

**Conclusion:** Temperature might increase the fetal brain tissue with early ultrasound examination; this could be a scientific fact but cannot explain why only some children are affected while others are not. Investigation of HSP proteins that regulate infant temperature needs more studies to explain its effect on the enzymes and infant brain.

**Keywords:** *Autism; Pathology; Ultrasound; Thermal Energy; Side Effects*

### Introduction

Autism spectrum disorders are neurodevelopmental disorders, many theories of its causation have been proposed but it is still incomplete [1]. Heritability is a major contributor to autism, around 90% of the risk of a child developing autism; it is unclear which genes are responsible [2].

Some chemical agents that cause birth defects are strongly associated with autism [3]. Exposures of children to vaccines have been proposed, as one of the causes of autism, these proposals are controversial and the vaccine hypotheses have no convincing scientific evidence [4]. It was Dr. Leo Kanner, a psychiatrist at Johns Hopkins University who wrote the first paper applying the term autism to a group of children who were self-observed and had severe social, communication, and behavioural problems.

Autism occurs in about 4.5 out of 10,000 live births. Autism is 3 to 4 times more likely to affect males than females. Some studies suggested that 1 to 150 children will have autism [5-13]. During infancy, many begin to rock and /or bang their head against the crib; other children exhibit includes arching the back away from their caregiver to avoid physical contact. In addition, dysfunctional behaviours (i.e.

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repetitive, non- goal directed behaviour, such as rocking, hand-flapping), self-injury (e.g. hand-biting, head banging), sleeping and eating problems, poor eye contact and attention deficits might be found [5-13].

Approximately 25% have seizures for the first-time during puberty which may be due to hormonal changes [5]. Common characteristic among autistic children is the individual's insistence on sameness; insistence on routines; drinking and eating the same food item at every meal; wearing certain clothing; using the same route with the same people; if one is changed, they become upset and agitated. There is no adjective which can be used to describe every type of person with autism because there are many forms of these disorders [5-13].

Some of the autistic distinct disorders shown by researchers include: Asperger syndrome, fragile x syndrome, Landau-Kleffner syndrome, Rett syndrome, and Williams's syndrome, the majority have heart problems [5-13].

The fragile x type is which the long arm on the X chromosome is constricted, 15% of people in this group exhibit autistic behaviours [5-13].

Researchers have located several left hemisphere brain abnormalities in individuals with autism; the reason is not known nor is the influence they have on behaviour.

With respect to brain structure, some investigators examined post-mortem brains of several autistic individuals and located two areas in the limbic system which are underdeveloped the amygdala and hippocampus. These two areas are responsible for emotions, aggression, sensory input, and learning.

The researchers also found a deficiency of Purkinje cells in the cerebellum. Using Magnetic Resonance Imaging Dr. Courchesne has found two areas in the cerebellum, vermal lobules VI and VII, which are significantly smaller than normal in autistic individuals. Interestingly, there are some autistic individuals whose vermal lobules VI and VII are larger than normal. Once or both of these areas of the cerebellum are believed to be responsible for attention [5-13].

It is thought that a viral infection or an environmental toxin may be responsible for damaging the immune system, there is also evidence of a genetic association to a compromised immune system, and researchers have found that many autistic individuals have a decreased number of helper t-cells which help the immune system fight infection [5-13]. The majority seem to have impairment in one or more of their senses, especially the auditory sense.

Vitamin B6 taken with magnesium has been shown to increase general well-being, awareness and attention in approximately 45% of autistic children [5-13].

Researchers have shown that some autistic individuals have excessive amounts of Candida albicans yeast in their intestinal tract and that good bacteria might be destroyed by the use of antibiotics. As a result, the yeast grows rapidly and releases toxins in the blood; and these toxins may influence the functioning of the brain [5-13].

Teratogens are environmental agents that cause birth defects [VI]. These include exposure of the embryo to thalidomide, valproic acid, or misoprostol, or to rubella infection in the mother [6].

All known Teratogens appear to act during the first 8 weeks from conception [3].

Pesticides such as dicofol, diazinon, chlorpyrifos, and endocal fan have been shown that more likely to give birth to children with autism if the mother is exposed to them [14-17].

Other causes were studied by scientists include maternal antibodies, fetal testosterone, stress fetal hypoxia during childbirth, immune system abnormalities, allergies, drugs, exposure, vaccines, infections, heavy metals [4,9,18,19,21].

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Today most researchers theorize that autism is caused by a complex interplay of genetics and environmental triggers. A far simpler possibility worthy of investigation is the pervasive use of ultrasound which can cause some thermal effects and might alter the genetic makeup [22].

The notion that claims to show that exposure to ultrasound in utero does not cause any significant abnormalities in the offspring is misleading, these studies can be criticized on several grounds including the lack of control population and/or inadequate sample size, and exposure after the period of major organogenesis; this invalidates the World Health Organization (WHO) conclusions regarding the safety of ultrasound [22].

Early studies showed that subtle effects of neurological damage linked to ultrasound were implicated by an increased incidence in left-handedness in boys and speech delays [23].

In August 2006, Dr Pasko Rakic, Chair of Yale School of Medicine's Department of Neurobiology, announced the results of his study on mice and it showed that Damage to brain cells increase with longer exposure to ultrasound [24].

### Problems with sound and heat

The FDA warned in 2004, that ultrasound even at low levels showed it can produce physical effects in tissue such as jarring vibrations and arise in temperature [25]. This is consistent with research conducted in 2001 in which an ultrasound probe aimed directly at a miniature hydrophone placed in a woman's uterus recorded sound as loud as a subway train coming into the station [26]. Researchers have shown that rise in temperature of fetal tissue is a fact even if the mother cannot feel it, and heat can cause significant damage to a developing fetus's central system [27,28].

Cornell University researchers proved in 2001 that ultrasound damages fetal brains in-small Mammals [9,29], When birth defects occurred in the lab tests on mammals, the acoustic output was usually high enough to cause considerable heat [9,30].

A study reported in the journal of the American Medical Association (JAMA) found that women who used hot tubs or saunas during early pregnancy face up to triple the risk of bearing babies with spina-bifida or brain defect [31].

### Heating: The thermal index

Sound propagates through a medium by means of oscillatory transfer of elastic energy. After the medium is compressed during the acoustic cycle which occurs 1 million times/second for a 1 MHz transducer, it does not return all of the energy when it expands again. The lost energy is converted to heat and is responsible for the absorption of sound during its passage through tissue. Absorption is generally the major contributing factor to attenuation in ultrasound imaging. Once the energy is absorbed by tissue, the result is a temperature rise. The degree to which the temperature rises depends on the conductivity and specific heat of the tissue, as well as the body's cooling system (Blood flow). It seems reasonable to assume that local temperature rises of less than 1°C to a mother or a fetus will be without harm as long as the threshold is less than 1.5°C [32,33].

### Cavitations: The mechanical index

Cavitations are the formation, growth and collapse of bubbles due to mechanism non-thermal energy or thermal energy and this can produce bio effects on tissue; ranging from reversible modulation of cell membrane to the complete destruction or even ionization of tissue [32,34]. There are stable and unstable (transient) cavitations one deals with any liquid that is saturated with gas such as water or blood and the other deals with much more violent process in which bubble is created during the refractory phase of the acoustic cycle and collapses during the next compression phase [32,34].

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Epidemiologic studies most literature regarding epidemiology was focused on birth weight, childhood malignancies, neurological development, dyslexia, handedness, and speech development.

### Birth weight

The low birth weight in some lab animals is well documented in regards to the ultrasound bioeffect.

Human birth weight data have been reported in many epidemiologic studies and have created some concern, especially when Doppler was used [35,36].

### Childhood malignancies

All the studies to date showed no associations between *in-vitro* ultrasound exposure and childhood malignancies [37,38]

### Neurologic development and dyslexia

Dr stark, *et al.* found a relationship between the use of ultrasound examination and Dyslexia [39], while Norwegian randomized controlled trials on routine ultrasound in pregnancy looked for possible adverse effects of ultrasound on the fetal brain and possible association of left-handedness, attention deficits, motor control, perception, hearing, visual acuity and neurologic development. Handedness was assessed because left-handedness is linked to dyslexia and attention deficit disorder, motor control and perception and found no association between ultrasound and dyslexia, poor vision or hearing or delayed neurologic development [40,41].

### Handedness

The literature is full of contradictions while some researchers found a possible link between a boy's non-right handedness and ultrasound exposure. Other scientists found no difference between ultrasound exposed and unexposed children with regard to hearing, vision, or behavioural disorders [41-44], while the Cochrane review has chosen not to present any data analysis or respond to the contradictions [45], one wonder if all these research papers are reliable.

### Speech development

Campbell study reported that the odds of suffering from delayed speech were 2.8 ( $p = 0.001$ ) times higher among children who were exposed to ultrasound at least once during pregnancy. The Norwegian and Swedish studies showed that a possible association with delayed speech development is found [46,47].

### Material and Methods

This study looked into 5800 obstetrics reports for those women who were signed consent forms to conduct a research using their data from the recent and previous reports. The women were given questionnaire lists to fill and return to the researcher by mail or email. The questions include are:

- The time of delivery day, or night
- Is the baby right or left-handed?
- Gender of the fetus
- How many ultrasounds did she have for one pregnancy? If multiple ultrasounds were done in which trimester she has it?
- Any other pathology noted after delivery
- Any sign of autism spectrum disorder up to 5 years old.

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4220 of those women had sonograms at 5 to 8 weeks, at 18 to 20 weeks, and at 28 to 30 weeks gestation for varieties of reasons. The author looked at the final radiologist’s reports and tabulated the result according to pathologies found by the sonographer and from the patient feedback data. No transvaginal sonogram was used on those patients.

This research was carried in multi centers in Canada, Saudi Arabia and Brunei. Ultrasound equipment used were ATL mark 12, Agilent Sonos 4500, Dasonic 1000 and 3000, ATL3000 and 5000 by Philips Company and IU22 Philips ultrasound. The author used multi frequency transducer 3 - 5 MHz, and TVS transducers 4 - 8 MHz Women age were between 19 to 42 years and the mean age was 30.5 years.

**Results**

From 5800 patients, the author obtained feedback from 4220 patients via mail and emails.

1580 patients did not respond, they either moved or declined to answer the question the author did not use their data in this research.

CW-Doppler, M-Mode, B-Mode, Angio color flow Doppler were used to study the fetal heart, placenta and cord blood flow, varicosity of the uterus, cord Doppler, and the cord insertion and the umbilical arteries at the bladder level. The result was tabulated (Table 1 and 2).

Total autism children reported were 23 children, 12 which were diagnosed with other anomalies.

<b>Pathologies found in 12 Autistic cases antenatal by ultrasound scanning</b>	<b>Number of cases</b>
Echogenic Bowel and absent left kidney	1 female
Echogenic kidney’s bilateral, 2vc	2 male, female
Echogenic lungs, 2vc	1 male
Echogenic foci in the heart	1 male
Polyhydramnios	2 male, female
Oligohydramnios	2 male, female
Hydrocephalus	1 male
Choroid plexus cysts bilateral	2 male, female
Nuchal translucency 7 mm in diameter	1 male

**Table 1**

Total number of patients n = 4220.

Total autism children n = 23 (9 females and 14 males)

13 autistic children were diagnosed with other anomalies in 18 weeks and 28 weeks gestation.

}5 female fetuses, and 8 males.

<b>Ethnicity</b>	<b>Number of cases with Autism</b>	<b>Percentages from the total numbers of patients examined 4220</b>	<b>Percentages from each group</b>
Mennonites in Alberta Canada n = 300 7.1%	8	0.18%	2.66%
Hatorites in Saskatoon Canada n = 300 7.1%	7	0.16%	2.33%
Native Indians in BC, and Alberta Canada n = 1000 23.6%	2	0.04%	0.2%
Caucasian n = 1220 28.9%	3	0.07%	0.24%
Malay in Brunei n = 820 19.4%	1	0.02%	0.12%
Middle Eastern from Saudi Arabia n = 400 9.4%	1	0.02%	0.25%
Chinese in Brunei n = 200 4.7%	1	0.02%	0.5%

**Table 2: Ethnicity groups.**

From patients feedback n = 23, 8 children with autism at age 4, and 14 children at age 5.

### Discussion

Temperature increases present a risk factor to developing fetus especially in early stages of life. An individual's body temperature varies throughout the day due to various factors such as circadian rhythms, hormone, fluctuations and physical exertion. A core temperature of 98.6°f is important because that is the point at which many important enzyme reactions occur. Temperature affects the actual shape of the proteins that create enzymes, and if the protein shape changes occur, they are unable to do their jobs correctly. As factors such as the amount of heat or duration of ultrasound exposure increase, enzyme reactions become less efficient until they are permanently inactivated, unable to function correctly even if the temperature returns to normal [48].

Shivering and sweating are important mechanisms to balance the body temperature and to regulate the body temperature when it is too low. Shivering warms the body, and if it is too high, sweating balances it off. Fetuses cannot cool off by sweating; they have another defence mechanism as each cell contains the heat shock proteins (HSP) that temporally step the formation of enzymes when temperatures reach high levels [49].

Ultrasound heats bones and cartilage at different rates than muscles, soft tissues, and amniotic fluid [50]. As bones calcify, they absorb and retain more heat, the baby's skull can heat up 50 times faster than its surrounding tissue during the third trimester subjecting parts of the brain that are close to the skull to secondary heat that can continue after the ultrasound exam has concluded [51].

With activation of heat shock (HS) response, normal protein synthesis is suspended and survival is achieved at the expanses of normal development [52]. Despite the finding of many researchers of the possible effect of heating on the fetus the FDA approved an 8-fold increase in the potential acoustical output of ultrasound equipment [9].

Autism epidemic is more noticeable in the industrial countries, what all industrial countries do have in common is the increased use of the routine prenatal ultrasound, transvaginal use in early pregnancy, the use of entertainment sonography and to use the 3D to image the face for a picture. Autism also increases in countries with nationalized health care where virtually all pregnant women are exposed to ultrasound. The autism rates are even higher than in the USA [53]. High risk pregnancy patients receive many more scans, like once a month scanning for twins, diabetic women, those with a history of genetic disorders which ironically may raise their risk.

The use of Doppler ultrasound which is used to study blood flow and the baby's heartbeat has increased according to the 2006 database of systematic reviews and Doppler may do more harm than normal B mode scan [54].

Many Radiologists and Physicians claim that ultrasound benefits outweigh the risk, that statement is false and has no basis as much evidence is to the contrary. A large randomized trial of more than 15000 pregnant women, conducted by the RADIUS study group found that in low-risk cases, high-risk subgroups and even in cases of multiple gestations or major anomalies, the use of ultrasound did not result in improved outcome in the pregnancies [55]. The result showed 1884 male fetuses and 2336 female fetuses that the male fetuses had their placenta located to the right side of the uterus (RT posterior, RT anterior, RT Lateral, RT fundal anterior, and RT fundal posterior) in 94 - 97%, while the female fetuses had their placenta located to the left side of the uterus (Left posterior, left anterior, left lateral, left fundal anterior, and left fundal posterior) in 94 - 98% of the times.

It seems that there is a relationship between the placenta sidedness and fetal gender where this test was duplicated using blind study. One sonographer was doing the placenta location, and the other sonographer documenting the fetal gender with the routine antenatal scan. The result also showed that pyelectasis (Fetal Renal Pelvic Dilatation) is increasingly seen with female fetuses that have their placenta in the right side and in male fetuses that have their placenta in the left side of the uterus.

One Echogenic bowel in female fetuses with right- sided placenta with absent left kidney and 2 vessels cord.

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Two Echogenic kidneys were diagnosed in male and female fetuses again. The male had the placenta located in the Right lateral side of the uterus and the female had the placenta in the left lateral side of the uterus, and Male fetus with 2 vessels chords.

One Echogenic foci was diagnosed in the fetuses' heart. RT ventricle this male fetus had the placenta located posterior left lateral position.

2 fetuses were diagnosed with Polyhydramnios 1 male and 1 female both have their placenta differing when compared to their gender.

1 male fetus was diagnosed with hydrocephalus and had placenta located on the left side of the uterus (left posterior location).

4 fetuses were diagnosed with 2 vessels, 2 females and 2 males, they had placenta differing in site compared to gender.

2 fetuses diagnosed with bilateral choroid plexus cysts, one male and one female with differing placental sites compare to gender.

As we know from the literatures that Echogenic bowel, Echogenic kidneys, Echogenic foci in the heart, Polyhydramnios, bilateral hydrocele, absent kidney, 2 vessel cords, and choroid plexus cysts might link to genetic malformation beside other causes. So, the question is still unanswered.

Does the placenta site versus gender have anything to do with this link? Are there any internal or external factors that lead to the site of implantation and forming of the placenta? If we diagnose many pathological problems with this method can other syndrome such as autism be one of the side effects of this placental change. Is it possible that repeated sonograms in early pregnancy be one of the factors that cause autism? This research is inconclusive and a large study is requiring proving the link between thermal energy and autism.

The feedback was focused on those patients with autism spectrum disorder children. The author took the survey and the feedback when the children reached 4 and 5 years of age to give a chance to more visible autistics behaviour to surface if any. The autism for those children was diagnosed and documented by a hospital psychiatrist and psychologist nurse.

We found 8 children at age 4 and 14 children at age 5 with autism.

Table 1 showed 23 autistic children from the total patients of 4220 is 0.54%.

12 of those children were diagnosed with other anomalies antenatal at age 18- and 28-weeks gestation. This indicated that almost 52% of the autistic children in this group have some form of abnormalities and are used as genetic soft markers in many literatures; therefore, the link between autism and genetics is very strong. The sonographers should ask the patients if they have any child or relative with autism and focus on those pathologies mentioned in table 1.

Table 2 shows the ethnicity of the 23 autistic children 300 Mennonites and 300 Hatorites were examined, they stand at 7.1% of the total patients. There were 8 Mennonites children and 7 Hatorites autistic children, and that is 0.18% and 0.16% from the total patients and 2.6% and 2.3% from each group respectively.

In the Native Indians group of 1000 only 2 autistic children were documented and both were Cree-Indians, and 100 Dene Indians. 1220 Caucasians with 3 autistic children, two belong to German families and one to Canadian family all three mothers had a Hypothyroidism problem. 820 Malay patients from Brunei had one autistic child and 200 Chinese patients from Brunei had one autistic child were in the group, both of those children belonged to mothers with hypothyroidism problems. Four hundred Arabic families had one autistic child, and both parents were diagnosed with hypothyroidism problems.

The author did not study the effect of Hyperthyroidism on autism. The hyperthyroidism might be relevant as the parents were taking medication (lithotroxeen) and the thyroid TSH was under control, but there might be a link between thyroid and autism and this should be investigated further.

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The effect of early ultrasound examination as one of the autism factors was also not proven in this study. From 4220 patients who had ultrasound examination in early gestation only 23 cases were reported with autism 0.54% as we know autism occurs in 4.5 out of 10,000 live births [5-13], our number showed that 0.54% is within acceptable limits and stand less than 1% of total patients studied.

The percentages increase in genetically restricted populations such as the Mennonites and Hatorites who practise very close marriages among the community.

The percentage of children with autism from the total number of patients were ranging from 0.02% - 0.18% and the percentage of children with autism from each group were ranging from 0.12% - 2.66%, 28.9% Caucasians from the total patients were examined followed by 23.6% Native Indians, Malay people 19.4%, Middle East (Arabic) 9.4%, Mennonites and Hatorites at 7% each and 4.7% were Chinese. From the 23 autistic children 9 were females and 14 were male given the ratios of 1.5 males to females. Those autistic fetuses with other pathologies were 13 (5 females and 8 males) ratios of 1.6 males to females.

It would be wrong, however, to assume that the risk of thermal energy does not exist if such effects are obvious in the treatment of tissue and remodelling cell behaviour in injury. Physiotherapies rely on the ultrasound bioeffect on soft tissues injuries. How can we be sure that such effects on cell behaviour do not occur during fetal sonography especially in the early stage of development of very small infants? In general, the biologic effects of ultrasound on tissue are dose dependent at the exposure levels used diagnostically, thus there is no safe threshold level.

Furthermore, the concept of ultrasound is problematic. Dose is the combination of exposure and tissue properties, both of which need to be known. There are a large number of parameters that determine the exposure conditions produced by a transducer at a given time. In principle, these can be determined, but in practice, the machines are capable only of relatively crude estimates of their own output.

The likelihood of bio-effects however depends on the interaction of this ultrasound field with the tissue. Even in principle, this is impossible to determine. Heating depends on tissue absorption, attenuation, and the uniformity of the speed of sound in tissue as well as the capacity of the tissue to cool itself by blood flow and heat conduction. These are all parameters that are unknown in a typical clinical setting. Even if we could evaluate some kind of dose, how would we calculate its fractionation? Would an examination at a certain exposure for 15 minutes carry the same risk as an examination of 30 minutes at half of that exposure?

In the absence of an exact science relating risk to ultrasound exposure and the unknown properties of tissue, we must resort to looking for evidence of biologic effects, in experimental laboratory models using *in vitro* and living tissue [32,33].

Norwegian study by Dr. Salvesen KA., *et al.* [40-42,47] suggested that it is unlikely that routine examination can cause harm to the developing fetal brain, but he did not research the thermal factor and cavitations.

It is possible that Campbell [23] study is not reliable as it was a small study; no information on ultrasound exposure was assessed and was not blind study. The misclassification of information on between cases and controls makes it difficult to rule out biases.

Limitation of this study might include follow-up offspring for only 5-years of age. It also didn't study other factors that might affect the fetus, particularly for the embryonic stage of prenatal development taking up to the beginning of the 3<sup>rd</sup> week in which rapid differentiation and embryogenesis of different organs and systems occur [56].

## Conclusion

Temperature increases the fetal brain tissue with early ultrasound examination; this might be a scientific fact but cannot explain why only some children were affected while others were not. The study of HSP proteins that regulate infant temperature needs more studies



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to explain its effect on the enzymes and infant brain. Routine prenatal ultrasound should be done only by experienced and registered sonographers or Sonologist.

Restricted genetic pool communities are prone to having children with autism. Autism is noted more in males than females at ratios of 1.5 - 1.6. Multi factors may be the causes of autism among them are genetic, ultrasound heat, and hormone imbalance. This study showed no strong association between diagnostic ultrasound exposure and autism during pregnancy, the sonographers should be very careful of using Doppler ultrasound unnecessary in early pregnancy. There seem to be an effect of placental location and fetal gender, where this was a secondary finding.

### Recommendations for ultrasound use:

- It should not used for entertainment purposes.
- Ultrasound machines should be set up so that the default (switch on) setting of the output power is low and increased only if necessary to obtain good information.
- Reduce exposure time as much as possible as many sonographers show the early fetus to parents and talk to them, do unnecessary Doppler and angio power study to impress parents or visitors especially in fetuses less than 8 weeks gestation.

This study contributes to advances in knowledge regarding Autism and the distribution in certain ethnic groups. The effect of ultrasound cavitations as other possible causes of Autism spectrum disorder, and let the physicians and sonographers to be aware of possible hazards on the fetus at early gestational ultrasound scanning.

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