

MEASLES VIRUS INFECTION WITHOUT RASH IN CHILDHOOD IS RELATED TO DISEASE IN ADULT LIFE

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Summary The presence of measles specific antibodies is usually taken as evidence of typical measles in the past; in the present study it was regarded as evidence of infection with measles virus, but not necessarily of the common disease accompanied by a typical rash. The association between a negative history of measles in childhood and certain diseases later in life was investigated by a historical prospective method, based on school health records combined with self-reporting in adulthood, and tests for specific IgG measles antibody. There was evidence of association between a negative history of measles, exposure in early life (possibly injection of immune serum globulin after exposure), and development of immunoreactive diseases, sebaceous skin diseases, degenerative diseases of bone and cartilage, and certain tumours. It is suggested that the presence of measles virus specific antibodies at the time of acute infection interferes with development of specific cytolytic reactions, and enables intracellular measles virus to survive the acute infection. If this hypothesis is verified, use of immune serum globulin after measles exposure has to be reconsidered.

Introduction

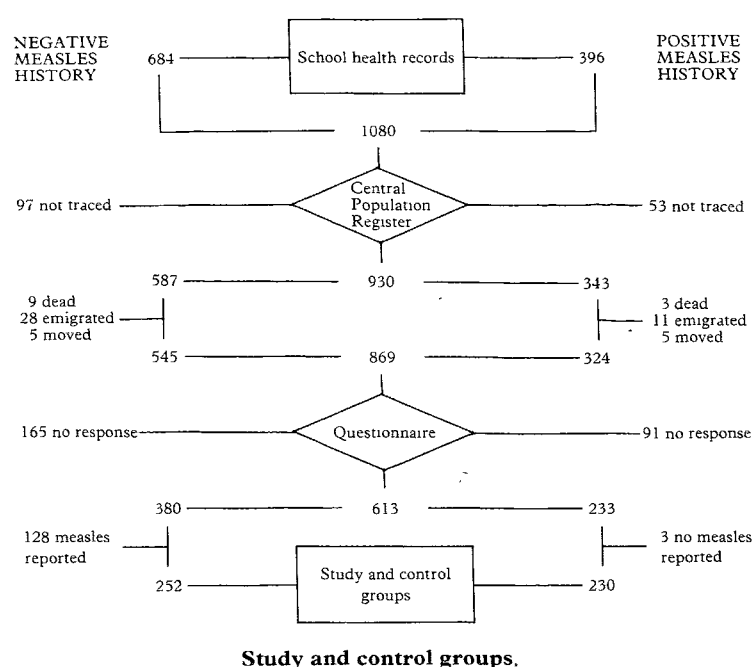
MEASLES is a highly communicable disease; in countries where routine measles vaccination is not practised, most children contract the disease in the first few years of life. Measles virus is also causally related to subacute sclerosing

panencephalitis (SSPE), a rare, slow-virus infection of the central nervous system, which mainly attacks children who have had measles in early childhood.^{1,2} In the USA, the number of SSPE cases has declined substantially, in parallel with the decline in measles cases observed after introduction of routine measles vaccination.³

The role of measles virus in multiple sclerosis (MS) has been investigated intensively, without conclusive results. If MS is related to measles virus, one would expect an association with measles infection unusually late in life. This is supported by the fact that MS mainly affects individuals with early birth order positions (ie, number 1 or 2 in a family).⁴ Early birth orders tend to delay exposure to an infectious agent, from early childhood to a later age, and vice versa.

Adults who have not had measles have either escaped exposure, or have responded without manifesting the pathognomonic rash. In general, the presence of measles virus antibodies is taken as evidence of past infection;⁵ in the present investigation, it was regarded as evidence of viral infection, but not necessarily of clinical measles.

The pathogenesis of the measles rash is not completely understood, although certain facts have been established. Thus, circulating antibody is usually first detected 24–28 hours after onset of the rash. Children with agammaglobulinaemia are capable of manifesting a rash and immunity,⁶ whereas infection in children with impaired cellular immunity may result in giant cell pneumonia without a rash.⁷ Measles virus antigen has also been shown to disappear from skin cells 3–4 days after onset of the rash.⁸ It is assumed, therefore, that the rash is caused by a cell-mediated immune reaction, which damages cells infected with measles virus.⁹ If this assumption is correct, absence of a rash may imply that intracellular virus escapes neutralisation during the acute infection, and this, in turn, might give rise to



development of diseases subsequently. Absent rash might also be an early expression of congenital impairment in cell-mediated immunity, which itself causes diseases later in life. The present study was done to investigate the possible association between absence of a measles rash in childhood (which would have been recorded as a negative history of measles) and certain adult diseases.

Methods

A historical prospective method was used, based on school health records combined with self-reporting in adulthood. The individuals investigated had attended State schools in the municipalities of Copenhagen and Gentofte. Gentofte is situated within the Copenhagen metropolitan area, but the population tends to have a higher socioeconomic status. In Copenhagen, records were available for individuals born in 1941 onwards, and in Gentofte for 1947 onwards.

Individuals with a negative history of measles according to school health records were identified in Gentofte and Copenhagen; the control group comprised individuals with a positive history of measles in Gentofte. The Gentofte study and control groups were matched for age and sex; the Copenhagen group was established to investigate whether the results represented an isolated Gentofte phenomenon. For each individual, name, date of birth, and birth order position were established. A search was then conducted in the Central Population Register, and individuals with a known address in Denmark were asked to complete a questionnaire on measles and other diseases. Two groups were established based on the replies: a study group with a negative history of measles and a control group with a positive history of measles (see figure). All information supplied on diseases (excluding accidents, common infectious

TABLE I—MEASLES STATUS IN GENTOFTE AND COPENHAGEN

	Gentofte		Copenhagen	
	School records (%) (n = 1989)	Combined with self-reporting (%)	School records (%) (n = 4320)	Combined with self-reporting (%)
Measles <8 yr	67	69	80	81
Measles 8–10 yr	13	15	5	7
Measles >10 yr	3	6	1	2
Cumulative incidence	83	90	86	90
No measles	17	10	14	10

Based on school health records, 173 questionnaires from Gentofte, and 207 questionnaires from Copenhagen.

TABLE II—BIRTH ORDER POSITION AND AGE AT CLINICAL MEASLES

Birth order position	No measles (n = 252)	Measles <8 yr (n = 1305)	Measles >8 yr (n = 262)
1 + 2	72%	80%	84%
3 +	28%*†	20%*	16%†

* $p < 0.01$, χ^2 test

† $p < 0.005$, χ^2 test

diseases, appendicectomy, and tonsillectomy), was checked with physicians or hospitals involved.

In order to evaluate information on measles in general given in school health records, 1989 records from Gentofte and 4320 from Copenhagen were analysed with respect to history and date of infection. The possible influence of birth order position on the occurrence and timing of measles infection was assessed from records of 1305 individuals who had measles under the age of 8 years (ie, before school entry in Denmark), and from 262 who had measles at the age of 8 years or older. Sera from 56 Gentofte residents with a negative history of measles, and from 59 with a positive history, were tested for specific IgG measles antibody by enzyme-linked immunosorbent assay (ELISA) technique.¹⁰ Detailed results will be reported elsewhere. Fisher's exact test or χ^2 test was used for statistical evaluation.

Results

86% of individuals (930 out of 1080) were traced from the Central Population Register (see figure). Response to the questionnaire was 71% (613 out of 869) after one reminder. The final group comprised 252 individuals with a negative history of measles (101 from Gentofte and 151 from Copenhagen). Mean age of the study groups was 38 years (32 years in Gentofte, 41 years in Copenhagen).

According to school health records, combined with self-reporting in adulthood, the cumulative incidence of measles (90%) was similar in the two populations studied (table I). The populations differed in relation to age at measles infection, in that Copenhagen children were younger than Gentofte children. Birth order position of number 3 or more occurred more frequently in those with a negative history of measles than in those with a positive history (table II); there was no difference between the Gentofte and Copenhagen groups. Specific IgG antibody was detected in 53 out of 56 Gentofte individuals with a negative history of measles, and in all 59 controls.

The diagnoses reported in the questionnaire, and verified by physicians or hospitals, were classified as shown in table III. This also shows the number of individuals in each category, and cumulative incidences in the study and control groups. There is a highly significant association between a negative history of measles and four disease categories: immunoreactive diseases, sebaceous skin diseases, degenerative diseases of bone and cartilage, and tumours (excluding cervical cancer and skin tumours). There was no difference in the results from Copenhagen and Gentofte. These four disease categories were designated "non-measles associated disease". Of 252 individuals with a negative history of measles, 60 (24%) had seventy three non-measles associated diagnoses. This group comprised 33 females and 27 males. Of 230 controls, eleven non-measles associated diagnoses were found in 11 individuals (5%). Thus the risk of acquiring non-measles associated disease was increased by 20% among individuals with a negative history of measles (10% of the population, see table I). This corresponds to a cumulative incidence in the general population of approximately 2%.

TABLE III—NUMBER OF INDIVIDUALS WITH VARIOUS DISEASES ACCORDING TO POSITIVE OR NEGATIVE HISTORY OF MEASLES

Diagnoses	252 individuals (Copenhagen and Gentofte) with negative history of measles*		101 individuals (Gentofte) with negative history of measles		230 controls (Gentofte) with positive history of measles†
	No (%)	p‡	No (%)	p‡	No (%)
Immunoreactive diseases	19 (8)	0·005	9 (9)	0·008	5 (2)
Sebaceous skin diseases (incl light induced eczemas)	28 (11)	<0·001	11 (11)	<0·001	4 (2)
Miscellaneous skin diseases	7 (3)	..	5 (5)	..	11 (5)
Skin tumours	5 (2)	..	2 (2)	..	6 (3)
Cervical cancer	8 (3)	..	3 (3)	..	1 (0)
Tumours other than skin and cervical cancer	15 (6)	<0·001	7 (7)	0·001	1 (0)
Degenerative diseases of bone and cartilage	11 (4)	0·005	6 (6)	0·004	1 (0)
Atopic diseases	15 (6)	..	9 (9)	..	17 (8)
Other diseases	21 (8)	..	7 (7)	..	14 (7)
Total no of diagnoses	129 ..	..	59 ..	..	60 ..
Non-measles associated diagnoses	73 ..	..	33 ..	..	11 ..
Total no of individuals with diagnoses	105 (43)	<0·001	45 (45)	<0·001	58 (25)
Individuals with non-measles associated diagnoses	60 (24)	<0·001	25 (25)	<0·001	11 (5)

*7 deaths not included: 3 suicides; 1 congenital heart disease; 3 cancer (testis; uterus; blast cell leukaemia).
†3 deaths (all suicides) not included
‡Fisher's exact test (one-sided p values).

Of 60 individuals with a negative history of measles who had non-measles associated disease, 20 (33%) had a birth order position of number 3 or more, a higher percentage than for all those with a negative history (see table II).

Immune Serum Globulin (ISG)

Although the questionnaire did not ask whether ISG was administered after measles exposure, this information was provided for 13 individuals with a negative history of measles (10 from Gentofte and 3 from Copenhagen). Of this small group, there were 3 cases of chondromalacia, and 1 each of lupus erythematosus and Scheuermann's disease; 8 had no non-measles associated diagnoses. In 2 cases of chondromalacia the diagnosis was established when the individuals were 17 years old; both had received ISG before the age of 1 year. In the third case, the diagnosis was established at the age of 36 years; ISG had been given after measles exposure at the age of 9 years.

Disease Categories (table III)

Immunoreactive diseases.—Among the 19 individuals with a negative history of measles, the diagnoses were: 9 arthritis; 4 iridocyclitis (1 with possible ankylosing spondylitis); 1 lupus erythematosus; 1 constrictive pericarditis; 1 thyroiditis; 1 connective tissue disease, with continued fever, arthralgia, and pulmonary and possibly cardiac involvement; 1 sarcoidosis plus Crohn's disease; 1 lung disease with breathlessness, hilar node involvement and radiographic pulmonary mottling. Other diagnoses in these 19 individuals included: 6 sebaceous skin diseases; 3 benign tumours (popliteal hygroma; sublingual cyst; mixed parotid tumour); 2 degenerative diseases of bone or cartilage (lumbar Scheuermann's disease, patellar chondromalacia); 1 peroneal nerve paralysis; 1 orchitis; 1 epididymitis; 1 nephrolithiasis; 1 splenomegaly. Among the 5 individuals with a positive history of measles the diagnoses were: 1 definite MS and 1 probable; 1 arthritis; 1 Crohn's disease; 1 rheumatic fever.

Sebaceous skin diseases.—Among the 28 individuals with a negative history of measles, the diagnoses were: 18 seborrhoeic dermatitis

and/or light-induced eczema; 4 severe acne; 2 rosacea; 2 perianal abscess (1 with fistula); 1 perioral dermatitis (rosacea-like); 1 lichen planus pilaris. Other diagnoses in this group included: 6 immunoreactive diseases; 4 alopecia; 3 generalised folliculitis; 2 pityriasis amiantacea; 2 anal fistula; 1 aphthous stomatitis; 1 tibial fibroma. Among the 4 individuals with a positive history of measles the diagnoses were: 3 seborrhoeic dermatitis; 1 miliaria rubra.

Tumours.—Among the 15 individuals with a negative history of measles there were single cases of the following: seminoma of testis; adenomatoid tumour of epididymis; mixed parotid tumour; epidermoid tumour of spinal cord; tibial fibroma; osteoid osteoma of femur; lipoma of spermatic cord; tumour of vocal cords; benign breast tumour; cholesteatoma; sublingual cyst; labial cyst, popliteal cyst; vaginal cyst; brainstem plaque detected by radioisotope scan and accompanied by central nervous system symptoms. The single diagnosis among individuals with a positive history of measles was exostosis of femur. Among those with a negative history of measles, 5 cases of malignancy were registered. 3 had died of cancer (blast cell leukaemia, carcinoma of uterus, carcinoma of testis), and therefore data on measles from school health records could not be combined with self-reporting. 2 cases had been combined with self-reporting: seminoma of testis (mentioned above) and basal cell carcinoma (other diseases, table III). Among those with a positive history of measles there were no registered malignancies other than cervical cancer.

Degenerative diseases of bone and cartilage.—Among the 11 individuals with a negative history of measles the diagnoses were: 5 Scheuermann's disease (1 with osteoarthritis of hip, 1 with arcolysis); 3 patellar chondromalacia (1 accompanied by iridocyclitis, 1 by Scheuermann's disease); 1 osteoarthritis of knee; 1 arcolysis; 1 otosclerosis. The single diagnosis among individuals with a positive history of measles was Scheuermann's disease.

Other diseases.—Among individuals with a negative history of measles who did not have non-measles associated diseases, some other diagnoses may be related to the phenomenon of missed measles rash, although statistical association was not shown for the following: nummular eczema; lichen planus; palmoplantar pustolosis; angular cheilitis; idiopathic lymphoedema; androgen insensitivity accompanied by possible pituitary tumour; pulmonary embolism (2).

Discussion

The data presented show that there is a highly significant association between the phenomenon of missed measles rash and later development of immunoreactive diseases, sebaceous skin diseases; degenerative diseases of bone and cartilage, and certain tumours.

The method of identifying individuals who have not had measles, based on school health records combined with self reporting in adulthood, has been shown to be valid. The cumulative incidence of measles in adults was studied in two areas which differed in age distribution of measles (as a result of socioeconomic factors), and was shown to be 90%. This is in agreement with another Danish epidemiological study on measles,¹¹ and with other observations.¹² It was also shown that most of those tested had specific measles antibodies, implying that they had been infected with measles virus. 3 individuals with a negative history of measles who were seronegative did not have any detectable disease. Thus, it is assumed that individuals who are at risk of developing non-measles associated disease are those who have been infected with measles virus, but who never manifested a rash. In Denmark, about 1% of 15–17-year-olds are seronegative for IgG by ELISA technique (C. H. Mordhorst, personal communication). This means that the group at risk constitutes 9% of the population.

If missed measles rash was an early manifestation of a congenital impairment of the immune system, this would not account for the association between late birth order positions and development of non-measles associated disease. The results relating to birth order positions indicate that an environmental factor, probably early exposure, is involved in pathogenesis, as seen in SSPE. Nevertheless, the genome (tissue type, immunological response, sex) may also be involved in pathogenesis, particularly in the expression of non-measles associated disease. In MS, late exposure is a characteristic feature, indicating a different pathogenesis from non-measles associated disease (and SSPE). Early exposure to measles virus probably indicates early exposure to other antigens which may also be involved in pathogenesis, either in conjunction with measles virus or alone.

Measles virus has also been implicated in the pathogenesis of systemic lupus erythematosus^{13,14} and Paget's disease.^{15,16} Results of an immunofluorescence study of skin biopsy specimens from patients with measles rash may shed some light on the association with diseases of sebaceous glands and hair follicles; in most cases foci of measles virus antigens were observed at these sites.⁸ The association between some of the well established diagnoses among the non-measles associated diseases and data on measles history from school health records, is under investigation.

The association between a negative history of measles, early exposure (possibly injection of ISG after suspected exposure), specific measles antibodies in adulthood, and non-measles associated diseases, suggests that the presence of measles virus specific antibodies at the time of infection interferes with the common immunological response to measles virus, especially with the development of specific cell-mediated immunity (and/or other cytotoxic reactions). Intracellular measles virus may then survive the acute infection, and cause diseases which develop in adulthood. Possible mechanisms, which may function singly or together, include: reactivation of measles virus, immunological reaction against the measles virus-cell complex, suppression of immunocompetent cells caused by persistent measles virus infection, and measles virus induced changes in the host cell genome.

Some features of measles virus infection may be relevant to the proposed pathogenesis. In acute infection, the spread of measles virus involves many organs, but with a strong predilection for lymphoid tissues and leucocytes. Children with acute measles have widespread immunodeficiency, attributable to reduced numbers of leucocytes and impaired lymphocyte function. Measles virus also has the ability to initiate persistent infection, as seen in SSPE, in which virus has been isolated from brain and lymphoid tissue,^{17,18} and in laboratory experiments in which persistent infection can be established in vitro in both T and B lymphoblasts.¹⁹ Nuclear DNA can integrate genomes of measles virus.¹⁴ T cells have surface binding sites for measles virus.²⁰ Host membrane antigens have been recognised in the envelope of measles virions,²¹ and the surface membranes of infected cells express two of the measles virus glycoproteins.²² Adding specific antibody to a cell culture infected with measles virus effectively removes viral antigens from the cell surface, while protracted exposure of acutely infected cells to measles virus antibodies results in a cell population that continues to express measles virus antigens internally, but not at the cell surface. Such cells are also refractory to immune lysis.²³ Specific antibody not only strips off surface viral determinants, but also alters intracellular viral

poplypeptides.²⁴ Observations in vivo also indicate that the presence of specific antibody may interfere with the typical reaction to measles virus. Thus, measles may be prevented or modified after exposure by passive immunisation with ISG, while antibody injected into the skin prevents development of the rash at the injection site.²⁵ The decreasing maternal antibody levels in children under 1 year of age are inversely related to increasing responsiveness of infants to measles vaccine.¹² In those who received a primary vaccination against measles before 10 months of age, revaccination several years later is often unsuccessful,²⁶ indicating that immunisation performed while antibody is present may induce a long-term suppressive effect.

Apart from serological studies, the common assumption that essentially everyone contracts measles is based on observations made during virgin soil epidemics.²⁷ The cumulative incidence of measles in adults in the present study is approximately 10% lower than that in virgin soil epidemics,²⁸ which might call into question the validity of the method used to identify individuals with a negative history of measles. It is important to remember, however, that the difference between virgin soil epidemics and measles in endemic/epidemic areas, is that neonates in virgin soil areas have not acquired maternal antibodies. Measles has been described in babies newborn to susceptible mothers, suggesting that inability to produce a rash is not necessarily associated with a young age.^{29,30} The lack of measles cases in children under 1 year of age in endemic/epidemic areas may well explain the difference in cumulative incidences, provided that children who fail to develop a rash after measles infection do not contract measles later in life. The association between a negative history of measles and early exposure in this study, and the difference between virgin soil epidemics and measles in endemic/epidemic areas, support this view.

Several types of evidence need to be examined before one can accept the hypothesis that measles virus causes non-measles-associated disease. It is necessary to search for measles virus antigens or genomes, and to assess immunological function, in particular cytotoxic reactions to measles infected cells in patients with non-measles associated disease. Perhaps most importantly, it is necessary to understand the fate of measles virus in vivo when ISG is administered after exposure. If the hypothesis that passively acquired antibodies constitute a risk factor is verified, the use of ISG after measles exposure has to be reconsidered. Measles vaccine contains live measles virus, but should be safe when given after disappearance of maternal antibodies. Measles can be controlled by large-scale vaccination, and where this is employed successfully the frequency of non-measles associated disease should be considerably reduced.

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PRENATAL DIAGNOSIS OF NEURAL-TUBE DEFECTS WITH A MONOCLONAL ANTIBODY SPECIFIC FOR ACETYLCHOLINESTERASE

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Summary An immunoassay for acetylcholinesterase (AChE), based on a monoclonal antibody (AE-2), gave the following results when applied to a panel of amniotic fluids: (a) among 651 samples with normal outcome and normal alphafetoprotein (AFP) values there were 2 (0.31%) false positives; (b) of 9 samples with normal outcome and raised AFP values 1 had a raised AChE titre; (c) all 48 samples from anencephaly cases had raised AChE values; (d) among 49 samples from open spina bifida cases (2 of which had normal AFP values), 48 had raised AChE titres. It is suggested that a monoclonal-antibody-based immunoassay may displace polyacrylamide gel electrophoretic analysis of AChE as a complementary test to AFP in prenatal diagnosis of neural-tube defects, since it is a quantitative test largely independent of operator skill and experience.

Introduction

POLYACRYLAMIDE-gel electrophoresis of amniotic-fluid cholinesterase isoenzymes has proved a useful adjunct to alphafetoprotein (AFP) assay in the second-trimester prenatal diagnosis of neural-tube defects.¹⁻⁴ In general, amniotic fluids from normal pregnancies have a single cholinesterase band attributable to non-specific cholinesterase (pseudo-cholinesterase), whereas those from pregnancies where the fetus has anencephaly or open spina bifida display an additional faster-migrating band of acetylcholinesterase (AChE). A collaborative study⁵ which investigated the potential of gel-electrophoretic cholinesterase analysis of samples with elevated amniotic-fluid AFP demonstrated that this technique could reduce the number of AFP-based false

positives without significant loss of sensitivity and suggested that it was a very satisfactory secondary test.

The usefulness of AChE analysis as a primary test for neural-tube defects is limited because the two available methods have serious disadvantages. Gel-electrophoretic analysis depends on visual inspection of stained gels, and different operators may disagree on whether or not an AChE band is present. Densitometric methods can help to resolve this difficulty, but they are time-consuming and depend on equipment not readily available in most laboratories.^{6,7} Attempts to measure AChE by enzymatic methods have been confounded by the difficulty of finding substrates or inhibitors with absolute specificity for either non-specific cholinesterases or AChE,⁸ which would allow total cholinesterase activity to be resolved into its component parts. In view of the unsatisfactory status of enzymatic methods, most laboratories continue to use the qualitative, operator-dependent system of gel electrophoresis.

The solution to this problem would be to devise an immunoassay in which an antiserum to AChE allowed this isoenzyme to be measured directly in the presence of non-specific cholinesterases. The availability of a monoclonal antibody to AChE,⁹ which does not cross-react with non-specific cholinesterases, has now made this possible.

Methods

All amniotic fluids for AChE assay (both immunoassay and polyacrylamide-gel electrophoresis) were taken from storage at -20°C. AFP assays had been done on receipt of fluids,¹⁰ and the values recorded at the time had been interpreted in terms of the gestation-dependent cut-off limits proposed by the UK Collaborative Study.¹¹ The 651 normal fluids represented a sequential series of the most recent samples on which the outcome was known to be an infant without an overt birth defect.

Hybridoma cells secreting the IgG₁ monoclonal AE-2 were obtained from the American Type Culture Collection (Rockville, Maryland, USA). AE-2 was raised against purified human red-blood-cell AChE and shown by immunocytochemistry to react with human neuromuscular junctions as well as junctions from a number of other species, including the calf.⁹ Hybridoma cells were grown in RPMI 1640 medium with 0.2 units/ml porcine insulin, 1 mM oxaloacetic acid, 0.45 mM sodium pyruvate, and 5% fetal calf serum. Cells were then resuspended in serum-free RPMI 1640 for 48 h, and the supernatant containing monoclonal antibody was

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