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Neurologic and psychiatric correlates of leukemia

Robert Edward Taubman
University of Nebraska Medical Center

THE NEUROLOGIC AND PSYCHIATRIC CORRELATES OF LEUKEMIA

Robert E. Taubman

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Introduction*

Our concern with the present problem stems from 1) an interest in the broad field of the neurological and psychiatric aspects of hemtological disorders; and 2) the fact that there is no single source to which one may refer in evaluating these particular complications or correlates in the specific area of the leukemias. The advent of new treatment methods (2, 8, 23, 27, 34), albeit palliative in nature, makes the recognition of the neurologic/psychiatric aspects of this group of hematologic diseases even more cogent because we now know that intracranial involvement in leukemia is not the rare phenomenon it was once thought to be. Therefore, it is our purpose herein to collate the pertinent, available information.

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THE NEUROLOGICAL AND PSYCHIATRIC CORRELATES

Nervous System Signs and Symptoms.

According to Yohe (36), prior to Schwab and Weiss' work in 1935, there were reports of 146 cases in which there had been some evidence of central nervous system involvement on pathologic examination. "Many of those cases had shown no clinical signs or symptoms suggestive of neurologic disease." Garvey and Lawrence (11) reported facial diplegia in leukemia. Viets and Hunter (32), Diamond (9), and Schwab and Weiss (29) reported cases of facial paralyses. Schwab and Weiss found neurologic symptoms in 20.5% of their 334 cases; they reported that cranial nerve paralyses and anesthesias were the commonest initial symptoms of intracranial involvement by leukemia.

Brandt (1) reported neurologic manifestations in 18 of 206 patients or an incidence of 8.6%. Nordlander (26) indicated that 27 of 154 patients or 17.5% showed neurologic signs or symptoms.

Leidler and Russell (19) found that 34 cases of a total of 67 which they reviewed showed neurologic signs and symptoms attributable to leukemic disease. In 11 of their 37 patients considered as a random group there were such signs and/or symptoms.

Wells and Silver (33) state that 42.9% of 59 patients showed neurologic signs or symptoms during the course of illness.

Sullivan (30) reviewed 9 cases in the English literature during the period 1920-1948 ("pre-chemotherapeutic era") in which

there were significant neurological signs or symptoms.

Williams, Diamond and Craver (35) state that 49% of their 1,864 leukemic patients showed cerebral involvement.

Review of the literature is difficult from the standpoint of enumerating percentages of various neurological signs and/or symptoms. Nonetheless, it is of interest to summarize the available material.

Schwab and Weiss (29) indicate that "from 25-50% of all cases of leukemia exhibit some clinical sign of neurologic involvement."

In 38 cases, Leidler and Russell (19) observed that headache was the most common symptom in 19; vomiting occurred in 12 of the 38 patients. Papilledema was observed in 5 of 38 cases; headache and papilledema in 2 cases among a total of 40. According to Leidler and Russell, the signs and symptoms of increased intracranial pressure "were present in only a small number of cases, although there were significant pathologic changes in the brain resulting from the leukemic disease in 92%." Hemiplegia occurred in 11 of 65 cases. Paralysis of one or more cranial nerves was noted in 12 cases and was known not to be present in 53 cases. Disturbances of vision, vestibular and auditory manifestations, as well as convulsive episodes occurred in 10% or less of the cases. In all, the most frequently recorded neurologic sign was a change in the deep or superficial reflexes (18 patients). Leidler and

Russell state that the incidence of neurologic signs or symptoms was 35%.

Wells and Silver (33) report that 52.4% of their 42 patients dying of leukemia had 27 episodes of nervous system disease; of the 21 alive at the time of their report, 2 patients each had 1 neurologic complication. They describe their complications as due to 1) hemorrhage and infection; 2) leukemic infiltration; and 3) miscellaneous disturbances. As described elsewhere in this report, the signs/symptoms observed are comprised of generalized convulsive behavior, fainting, vomiting, paresis, headache and change in mental state (slowing, drowsiness, somnolence, disorientation as to time and place, and coma).

Yohe (36) cites 3 cases reported by Schwab and Weiss (29), Creskoff (7), Litteral and Malamud (21) in which there were cranial nerve paralyses prior to clinical or hematological evidence of leukemia. Yohe (36) also cites 3 cases reported by Gauld (12) and one case by Murphy and Brody (25) in which the initial complaints were neurologic, commonly including back and extremity pain, as well as cranial and spinal nerve paralysis. Yohe presents a case showing appearance of neurologic symptoms prior to the clinical or hematological suggestion of leukemia. The presence and progress of an intracranial infiltrate do not always parallel the stage(s) of leukemia peripherally, according to Cramblett (6). Gilbert and Rice (13) present three cases of children with lymphatic leukemia which simulated acute bacterial meningitis.

Williams, Diamond and Craver (35) describe the occurrence of neurologic symptoms in their large series of leukemias (1,864 patients). Within a total group of 276 cases with neurologic complications, 140 patients were marked by intracranial hemorrhage, 51 showed cerebral complications, 31 had herpes zoster, 17 showed pituitary involvement, 13 had spinal cord complications (such as compression), 9 had cranial nerve involvement, 7 showed involvement of peripheral nerves and 8 patients showed central nervous system infection.

Dickenman and Chason (10) note that lesions of the peripheral nervous system, including the dorsal root ganglia, occur with a frequency (in their series of post-mortem studies) far greater than might have been anticipated by the clinical manifestations. Indeed, in their opinion, primary or secondary lesions of the peripheral nervous system should be suspected in patients with neoplastic diseases of the hematopoietic system.

Sullivan reports on a relatively new aspect of the neurologic correlates of anti-leukemic therapy with folic acid antagonists and adrenal steroids (30). There is an accumulating body of knowledge purporting to show a special syndrome occurring in leukemic children treated with such drugs as 6-mercaptopurine plus adrenocorticoids. Sullivan estimates that 25% of the leukemic children so treated at her hospital have shown this syndrome, whereas leukemic children untreated do not show these sequelae. Related findings are also being gathered elsewhere (4). Sansone

(28) has 2 cases with this syndrome. These treated children show signs of increased intracranial pressure, including irritability, headache, vomiting and meningismus. According to Sullivan, the signs are of a more diffuse neurologic nature, may include vascular hypertension, increased appetite and obesity being less frequent. The Boston experience indicates the possibility that, in children receiving anti-metabolites, the blood-brain barrier rejects the drugs, thus leading to increased intracranial pressure, the neurologic correlates comprising vomiting, headache, drowsiness, papilledema, separation of the sutures and increased CSF pressure. Contrary to Sullivan's experience, children in the Boston study who have received adrenal steroids have not shown increased intracranial pressure.

The role of papilledema as a neurologic sign is an equivocal one. Leidler and Russell (19) are of the opinion that in leukemia papilledema is not an indication of increased intracranial pressure; indeed, they found papilledema an infrequent occurrence. Leidler and Russell believe that this sign therefore can not be taken "as reliable evidence that there is concomitant significant pathological change in the brain." It is also to be noted that the pressure of the CSF is not always highly correlated with the presence of neurologic signs or symptoms in this disease (6).

Intracranial Hemorrhage.

Diamond's (9) report of 14 cases shows foci of leukemic cell infiltration into brain substance in 8 cases and these foci are described as frequently surrounded by hemorrhage.

Schwab and Weiss (29) reviewed 146 cases of central nervous system involvement in leukemia and found cerebral hemorrhage in 32.2% of their group.

Leidler and Russell (19) found grossly visible foci of hemorrhage in the brain in 47 of a total of 65 cases in which specific mention was made of an examination for this occurrence. In 36 of the brains, histologic study showed that the foci of hemorrhage were accompanied by infiltrations of leukemic cells. In their random series (31 cases), 19 cases were found to show grossly visible foci of hemorrhage. Hemorrhage in the brain of such proportion to be the immediate cause of death was a frequent complication and was found in 27 of 60 cases in which adequate information was available. In the random series, the incidence of cerebral hemorrhage leading to death was 9 of 31 cases.

In a series of 63 patients studied by Wells and Silver (33), intracranial hemorrhage was regarded as the severest and most frequent nervous system manifestation of acute leukemia. There were 13 episodes of intracranial bleeding in 12 patients, and 10 episodes appeared to be directly related to the death of the patients. Three patients survived an episode of bleeding and one of these died of a subsequent hemorrhage; the remaining two patients died

subsequently of other causes. In 4 of the 12 patients, a generalized seizure heralded the onset of bleeding, but other pre-hemorrhage symptoms and signs included fainting, vomiting, paresis, headache, and changes in mental state. All patients who died because of intracranial hemorrhage manifested a platelet count less than 25,000/cu.mm.

Williams, Diamond and Craver (35) indicate that 140 of their 1,864 leukemic patients showed clinical or pathologic evidence of intracranial hemorrhage. The hemorrhages were usually intracerebral (80%) and were of major proportions in 82% of their cases. The hemorrhages were most frequently associated with thrombocytopenia secondary to leukemic infiltration of the marrow. Both platelet count and marrow examination within one week of hemorrhage were available in 92% of the patients, and of these, 74% had platelet counts below 50,000/cu.mm. with moderate to complete leukemic infiltrations of the marrow. Another 16% had thrombocyte counts below 50,000/cu.mm. with moderate to marked marrow hypocellularity, usually in patients who had received marrow depressants.

In a total of 815 leukemic patients, Hunt, Bouroncle and Meagher (18) found 86 patients who demonstrated hemorrhage. They regarded hemorrhage in or about the central nervous system caused by thrombocytopenia as the most frequent neurologic complication of leukemia. The hemorrhages tended to be massive intracerebral, subarachnoid or intra-axial hemorrhages, associated with severe thrombocytopenia, usually with clinical evidence of hemorrhagic diathesis elsewhere. In this group, the hemorrhages were invariably fatal within a few hours or days.

Leukemic Infiltration.

Burns (3) is said to have been the first to report complications of the nervous system in leukemia. In 1927, Tromner and Wohlwill (31) reported 12 cases of leukemia and of these, 9 had neurologic complications. Autopsy studies showed microscopic evidence of invasion of the central nervous system in 11 of the 12 cases.

Each of Diamond's (9) 14 cases showed leukemic cell involvement of the meninges and pial vessels to some degree, and 8 cases showed foci of infiltration of varying size and wide distribution into the brain substance itself.

In 146 cases, Schwab and Weiss (29) found meningeal involvement in 17.8% of the cases; cerebral invasion in 15.7%; cranial nerve nuclei affected in 15.7%. Thirty per cent of the cases manifested involvement of more than one part of the nervous system.

In a total group of 67 cases, Leidler and Russell (19) found that infiltration of leukemic cells into the brain parenchyma, excluding those in the perivascular spaces, occurred in 42 patients. Among these 42 cases, the infiltrated mass measured 5 mm. or less in diameter in 24 patients; in 11 cases, the foci were greater than 5 mm. but not greater than 2 cm; and in 7 cases, the foci were greater than 2 cm. in diameter.

The foci of infiltration appeared hemorrhagic to gross inspection and were moderately soft in consistency. Wherever there was infiltration into brain parenchyma, leukemic infiltration of

the perivascular spaces always occurred. Forty-one of 67 cases showed "leukostasis" (engorgement of blood vessels with leukocytes in the complete or almost complete absence of erythrocytes); 24 of 31 random cases showed this phenomenon. Leukostasis was found in 9 brains without infiltration of the parenchyma.

Leidler and Russell also observed leukemic infiltrations into the cranial nerves, with cranial nerve VII most commonly affected, and in descending order: II, VIII, III, V and X, and XII.

In all, 92% of the cases studied by Leidler and Russell showed hemorrhage and leukemic cell infiltration, as did 83% of the random series.

Wells and Silver (33) found 11 episodes of leukemic cell infiltration, 8 occurring intracranially and 3 within peripheral nerves.

Individual cases of leukemic infiltration are reported by Munro (24), Viets and Hunter (32), Lipton and Bucy (20), Sansone (28), Hamilton and Elion (17), Yohe (36), and Sullivan (30).

Williams, Diamond and Craver (35) report a total of 8 cases of leukemia showing invasion and infarction, meningeal invasion and parenchymatous invasion by leukemic infiltrates.

Among the 815 leukemic patients evaluated by Hunt, Bouroncle and Meagher (18), 15 patients showed leukemic infiltrations.

Cramblett (6) presents an individual case of widespread leukemic infiltrations of brain and meninges.

Psychiatric Components.

Observations of patients with a wide variety of disease entities have attempted to correlate psychologic factors with peptic ulcer, essential hypertension, the various collagen diseases, as well as the reticulo-endothelioses, including the lymphomas. The psychologic and neurologic implications of certain diseases of the hematopoietic system have undergone extensive study and special mention need be made here only of those related to pernicious anemia.

Selye's work on the "Adaptation Syndrome" has suggested that non-specific stress may stimulate body alterations in various organ systems, including the gastro-intestinal tract and the circulatory system. Greene (14) and others have raised the question whether reactions of the reticulo-endothelial system may take place as an adaptive response to psychologic stress. Miller and Jones (22) have suggested the possibility that emotional factors may precipitate disease in a number of cases of myeloid leukemia.

Greene (14) studied 11 leukemia patients (along with a group of cases with lymphomas not here considered). His findings indicate that "in all. . . cases, the development and recognition . . .(of the disease). . .occurred while the patient was having to adjust to a loss of support." This loss is described as including loss of significant object relationships, especially the separation from a parent-figure, usually the mother or mother-figure. Death of the parent was the most frequent loss, but the loss might

also have occurred in the form of desertion or sibling rivalry. In addition, in most cases, there was a concurrent real or threatened emotional trauma, as in injury, operation, aging, retirement or changes in work.

Although Greene could not identify any special personality typology or common conflict situation in his patients, he noted that his cases usually manifested a wide variety of symptoms, such as anxiety and depression, pain, headache, anorexia, vomiting, constipation, etc; yet, these could not be related to the extent or activity of the leukemic process itself. It was Greene's opinion that psychological stress may have been a factor in the time of appearance and the severity of symptoms, as well as the reaction in the reticulo-endothelial system in each case. ". . .The pathological response in these patients may represent, in some way, another form of adaptation for responding to psychological stress. The organism may react to the psychological stress, as though to any noxious agent which has gained access to the body, by various manifestations of altered function of the reticuloendothelial tissues." Leukemia would be interpreted as a more autoplastic and more primitive adaptation than the psychogenic diseases which function through voluntary or vegetative control systems.

Greene, Young and Swisher (15) extended the above observations to a group of 19 female patients with leukemia (as well as 13 patients with lymphoma not included in this discussion). They infer that all of their cases had an unresolved attachment to

their mothers; further, that there were four personality types represented among the patients: "mothering", "clinging", "isolated", and "manly".

In the above cases, four years prior to the apparent onset of the disease, various types of losses, separations, or threats of separation took place. Half of such losses or separations are said to have occurred in the period of one year prior to the apparent onset. The loss included that of a parent, spouse or child by death or illness; also included were the menopause or a change of home. Significant symptoms prodromally were fatigue, weakness, sadness, anorexia and nausea. The majority of patients showed effects of sadness or hopelessness for weeks or months prior to the apparent onset. Moreover, episodes of exacerbations of the disease process were believed, in some instances, related to periods of psychological stress. The authors concluded that, in their opinion, one of the multiple conditions determining development of the disease might be separation from a key object or goal with ensuing depression.

Greene and Miller (16) studied 33 children and adolescents (less than 20 years of age) with leukemia. They confirm the hypothesis noted above concerning the relation between onset of leukemia and loss of, separation from or threat of separation from a significant object. Thirty-one of the 33 patients showed this relationship. Half of such loss/separations occurring during a two-year prodromal period took place within six months of apparent

onset of the disease. Moreover, 27 of the 33 mothers involved were depressed and/or anxious for weeks or months before evident symptoms occurred in the child.

CASE PRESENTATION*

This 6-year-old white girl was first admitted to a local hospital because of listlessness and flaccidity which appeared following a "cold" of three weeks' duration. On admission, in addition to the neurologic findings noted, there was evidence of a palpable apical thrill, cardiomegaly with systolic and diastolic murmurs, and splenomegaly. Hbg. was 3.3 gm%, RBC 1.15 million/cumm., WBC 11,000. She was treated with antibiotics and whole blood transfusions. Roentgenograms of the chest and abdomen revealed slight cardiomegaly, bilateral ventricular enlargement (predominantly right-sided) and pulmonary congestion bilaterally. A mass in the LUQ was noted and believed to be intra-abdominal. Bone marrow study revealed a pancytopenia probably due to marrow replacement. On 10/27/57, Hbg. was 5.6 gm%, RBC 2.5 million/cu.mm., WBC 3,100/cu.mm. Differential revealed 6 segs, 90 lymphs, 4 monos. Vitamin B-12 was added to treatment regimen. On 10/30/57, leukemia or neuroblastoma considered in working hypotheses.

On 11/1/57, Hbg. was 9.2 gm%, RBC 2.8 million/cu.mm., and WBC 1,600/cu.mm. with 100% lymphocytes. Reticulocyte count 0.1% or less. Cardiac findings limited at this time to slight systolic murmur throughout heart; no thrills. Spleen considered slightly diminished. Clinical course continued to show improvement.

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* Case by courtesy of Dr. J. M. Margolin, Omaha.

On 11/2/57, Hbg. 14 gm%, RBC 3.8 million/cu.mm., WBC 2,000/cu.mm. with 48 lymphs and 2 staff forms (based on 50-cell count). Pyelogram on 11/4/57 was normal. Mass in LUQ was read as "no doubt related to the spleen." Skull film interpreted as without evidence of increased intracranial pressure, without evidence of osteolytic lesions, and bony structures considered normal. Ecchymoses and petechiae were noted on child's shoulders and back; bleeding noted on hypodermic injections.

A bone marrow aspiration on 11/7/57 was a "dry tap". Hbg. 10 gm%, RBC 3.98 million/cu.mm., WBC 1,500/cu.mm. with 1 staff and 49 lymphs. Prednisolone added to treatment. Whole blood transfusions were given and Vitamin B-12 was discontinued. Clinical improvement noted.

On 11/12/57, "moon" facies noted. RBC 3.31 million/cu.mm., WBC 1,900 with 9 segs, 9 staff, 81 lymphs and 1 mono. Clinical improvement continued. On 11/16/57, Hbg. 13.5 gm%, RBC 4.0 million/cu.mm. Differential showed 47 segs, 2 staff, 51 lymphs. Dismissed from hospital on prednisolone. Hemogram on 11/30/57 was normal; platelet count was 75,000-100,000/cu.mm.

Patient was again hospitalized on 3/19/58 with presenting complaint of gingival bleeding. Hbg. 9.8 gm%, RBC 3.2 million/cu.mm., WBC 10,900/cu.mm. Differential: 33 segs, 4 staff, 63 lymphs. Platelet count: 40,000/cu.mm. Bone marrow aspiration interpreted as subacute lymphocytic leukemia. Aminopterin and prednisolone therapy instituted. During this second hospitalization, there were

gingival hemorrhages, hematuria, emesis, abdominal distention and possible bleeding from the lower GI tract. The child was described as listless and anorexic for "considerable" time periods. On at least two occasions, there was leukopenia of 650/mm. or less. However, she improved slowly and was dismissed on 4/28/58 on aminopterin and prednisolone.

Occasional frontal headaches were noted on or about 3/16/59. Hemogram at that time was: Hbg. 12.1 gm%, RBC 4.3 million/cu.mm., WBC 7,000/cu.mm. with 47 segs, 47 lymphs, 5 monos and 1 eosin. On 3/26/59, the patient was readmitted to a local hospital presenting with complaints of listlessness, headache and vomiting. The hemogram was normal. A diagnosis of right maxillary sinusitis was made and the child improved under treatment, including antibiotics, aminopterin and prednisolone. She was dismissed on 3/28/59.

At home, however, the child showed malaise and continued listlessness. She was then hospitalized on 5/4/59. Once again the presenting complaints consisted of listlessness, vomiting and headache. Diagnosis was bronchitis; treated and dismissed on 5/9/59.

Frontal headaches apparently continued. On 6/21/59, the child had a convulsive seizure, without hyperpyrexia. She was admitted to the hospital on 6/22/59. Pupils appeared dilated but were responsive to light. She was seen by neurological consultants. EEG on 6/22/59 showed: a record dominated by very high-voltage 1-3/sec. waves. Some asynchrony between hemispheres at times, but no definitely lateralizing indications. The record was classified

as showing marked diffuse slow abnormality. Dilantin ordered. On admission, she showed pitting edema of the lower extremities. Hbg. was 14.6 gm%, RBC 4.93 million/cu.mm., WBC 7,800/cu.mm. with 58 segs, 40 lymphs, 2 monos. UA showed a trace of albumin and 4-5 WBC/hpf., many hyaline casts. Steroids, anti-metabolites and diuretics given. Continued to show intermittent headache and vomiting. On 6/25/59, irritability continued and headaches were persistent. Convulsive seizure occurred following enema. Headaches and edema began diminishing. On 7/2/59, however, patient experienced a right-sided, temporary paralysis. Papilledema of "several diopters" was noted. On 7/8/59, papilledema, 3 diopters, noted in right eye,without papilledema in the left. Slight intermittent headaches continued. She was dismissed on 7/10/59.

She continued well, except for periods of depression and constipation, slight headaches and vomiting spells. On 7/19/59, she had a convulsive seizure, slowed respirations and was unresponsive. Hospitalized. Headaches continued, she was depressed, complained of pain; opisthotonos noted. Hbg. 13.7 gm%, RBC 4.54 million/cu.mm., WBC 12,100 with 79 segs, 4 staff, 11 lymphs and 6 monos. Serum electrolytes on 7/22/59 were normal as was the BUN. Patient showed nuchal rigidity and pain and she appeared in critical condition. She was transferred to another hospital, where a ventriculogram and posterior fossa exploration were carried out. Signs of increased intracranial pressure were noted on exploration. Roentgenograms revealed symmetric dilatation of the lateral

ventricles and dilatation of the third ventricle. No tumor was found. Continuous ventricular drainage was instituted. Pathologic diagnosis was lymphocytic leukemic infiltration of the pia arachnoid. On 7/28/59, there was a recurrence of seizures. A rubber ventricular drain was found to be obstructed and replaced in a subsequent burr hole procedure which was carried out to relieve the internal hydrocephalus. On 7/28/59, repeat bone marrow aspiration was interpreted as compatible with lymphocytic leukemia. A course of radiation therapy to the skull was given beginning on 7/27/59. She was dismissed on 8/18/59. Aminopterin continued.

On 10/17/59, the child was seen for ophthalmologic evaluation. No light perception noted. The optic nerves showed extreme atrophy with blurring of the margins, consistent with the optic atrophy secondary to papilledema. Conjugate deviation to the left side was noted, which may indicate a fresh irritative lesion in the left cerebral hemisphere. The retinas showed no infiltrates; the retinal arteries were described as small and constricted due to the fibrosis from the previous edema.

(N.B. This patient is at home now and said to be doing well.)

SUMMARY AND CONCLUSIONS

A. Nervous System Signs and Symptoms

1. From 18%-53% of the patients studied are reported as showing neurologic signs or symptoms.

2. The most commonly given neurologic signs or symptoms are related to:

a. Cranial nerve paralyses and anesthesias.

b. Change in deep or superficial reflexes.

c. Headache.

d. Vomiting.

3. The use of anti-metabolites in children may be associated with signs of increased intracranial pressure.

a. The possibility is raised that anti-metabolites do not pass the blood-brain barrier.

b. The role of steroids is equivocal.

4. Neither papilledema nor cerebrospinal fluid pressure may be highly correlated with the presence of neurologic signs or symptoms in leukemia.

B. Intracranial Hemorrhage

1. Considered by some investigators as the severest and most frequent nervous system manifestation of acute leukemia, and found in 7%-72% of all leukemias, often associated with severe thrombocytopenia.

2. A significant immediate cause of death in all studies and stated as antecedent cause of death in 29%-83% of reported deaths.

C. Leukemic Infiltration

Occurrence reported in from 2%-100% of all cases reviewed. Except for one study, found in high percentage of cases.

D. Psychiatric Components

Stress phenomena are considered part of the multiple conditions determining the development of leukemic disease.

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Case Presentation

A case is presented of a 6-year-old child who showed neurologic complications of leukemia, including leukemic infiltration of the pia arachnoid.

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