13 - 443 Frontotemporal Dementia

443 Frontotemporal Dementia

one study), migraine, or cardiac arrhythmias have all been implicated. Approximately one-quarter of patients experience recurrent attacks. Rare instances of permanent memory loss have been reported in patients with TGA-like spells, usually representing ischemic infarction of the hippocampus or dorsomedial thalamic nucleus bilaterally. Sei zure activity due to AD should always be suspected in this syndrome. The ALS/parkinsonian/dementia complex of Guam is a rare degen erative disease that has occurred in the Chamorro natives on the island of Guam. Individuals may have any combination of parkinsonian fea tures, dementia, and MND. The most characteristic pathologic features are the presence of NFTs in degenerating neurons of the cortex and substantia nigra and loss of motor neurons in the spinal cord, although recent reanalysis has shown that some patients with this illness also show coexisting TDP-43 pathology. Epidemiologic evidence supports a possible environmental cause, such as exposure to a neurotoxin or an infectious agent with a long latency period. One interesting but unproven candidate neurotoxin is the seed of the false palm tree, which Guamanians traditionally used to make flour. The amyotrophic lateral sclerosis (ALS) syndrome is no longer present in Guam, but a dement ing illness with rigidity continues to be seen. Rarely, adult-onset leukodystrophies, lysosomal storage diseases, and other genetic disorders can present as a dementia in middle to late life. Metachromatic leukodystrophy (MLD) causes a progres sive psychiatric or dementia syndrome associated with an extensive, confluent frontal white matter abnormality. MLD is diagnosed by measuring reduced arylsulfatase A enzyme activity in peripheral white blood cells. Adult-onset presentations of adrenoleukodystrophy have been reported in female carriers, and these patients often feature spinal cord and posterior white matter involvement. Adrenoleuko dystrophy is diagnosed by demonstrating increased levels of plasma very-long-chain fatty acids. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is another genetic syndrome associated with white matter disease, often frontally and temporally predominant. Diagnosis is made with skin biopsy, which shows osmophilic granules in arterioles, or increasingly through genetic testing for mutations in Notch 3. The neuronal ceroid lipofuscinoses are a genetically heterogeneous group of disorders asso ciated with myoclonus, seizures, vision loss, and progressive dementia. Diagnosis is made by finding eosinophilic curvilinear inclusions within white blood cells or neuronal tissue. Psychogenic amnesia for personally important memories can be seen. Whether this results from deliberate avoidance of unpleasant memories, outright malingering, or unconscious repression remains unknown and probably depends on the patient. Event-specific amnesia is more likely to occur after violent crimes such as homicide of a close relative or friend or sexual abuse. It may develop in

association with severe drug or alcohol intoxication and sometimes with schizophrenia. More prolonged psychogenic amnesia occurs in fugue states that also commonly follow severe emotional stress. The patient with a fugue state suffers from a sudden loss of personal identity and may be found wandering far from home. In contrast to neurologic amnesia, fugue states are associated with amnesia for personal identity and events closely associated with the personal past. At the same time, memory for other recent events and the ability to learn and use new information are pre served. The episodes usually last hours or days and occasionally weeks or months while the patient takes on a new identity. On recovery, there is a residual amnesia gap for the period of the fugue. Very rarely does selective loss of autobiographic information reflect a focal injury to the brain areas involved with these functions. Psychiatric diseases may mimic dementia. Severely depressed or anxious individuals may appear demented, a phenomenon sometimes called pseudodementia. Memory and language are usually intact when carefully tested, and a significant memory disturbance usually suggests an underlying dementia, even if the patient is depressed. Patients in this condition may feel confused and unable to accomplish routine tasks. Vegetative symptoms, such as insomnia, lack of energy, poor appetite, and concern with bowel function, are common. Onset is often more abrupt, and the psychosocial milieu may suggest prominent reasons for depression. Such patients respond to treatment of the underlying

psychiatric illness. Schizophrenia is usually not difficult to distinguish from dementia, but occasionally the distinction can be problematic. Schizophrenia generally has a much earlier age of onset (second and third decades) than most dementing illnesses and is associated with intact memory. The delusions and hallucinations of schizophrenia are usually more complex, bizarre, and threatening than those of demen tia. Some chronic schizophrenics develop an unexplained progressive dementia late in life that is not related to AD. Conversely, FTD, HD, vascular dementia, DLB, AD, or leukoencephalopathy can begin with schizophrenia-like features, leading to the misdiagnosis of a psychiatric condition. Later age of onset, significant deficits on cognitive testing, or the presence of abnormal neuroimaging suggest a degenerative condi tion. Memory loss may also be part of a conversion disorder. In this situ ation, patients commonly complain bitterly of memory loss, but careful cognitive testing either does not confirm the deficits or demonstrates inconsistent or unusual patterns of cognitive problems. The patient’s behavior and “wrong” answers to questions often indicate that they understand the question and know the correct answer.

CHAPTER 443 Clouding of cognition by chronic drug or medication use, often pre scribed by physicians, is an important cause of dementia. Sedatives, tranquilizers, and analgesics used to treat insomnia, pain, anxiety, or agitation may cause confusion, memory loss, and lethargy, especially in the elderly. Discontinuation of the offending medication often improves mentation. Frontotemporal Dementia ■ ■FURTHER READING Andrews SJ et al: Interpretation of risk loci from genome-wide asso ciation studies of Alzheimer’s disease. Lancet Neurol 19:326, 2020. Belloy ME et al: A quarter century of APOE and Alzheimer’s disease: Progress to date and the path forward. Neuron 101:820, 2019. Cummings J et al: Progress in pharmacologic management of neu ropsychiatric syndromes in neurodegenerative disorders: A review. JAMA Neurol 81:645, 2024. Graff-Radford J et al: New insights into atypical Alzheimer’s disease in the era of biomarkers. Lancet Neurol 20:222, 2021. Jack CR et al: Revised criteria for the diagnosis and staging of Alzheimer’s disease. Nat Med 30:2121, 2024. Schindler SE et al: Acceptable performance of blood biomarker tests of amyloid pathology: Recommendations from the Global CEO Ini tiative on Alzheimer’s

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Frontotemporal

Dementia Frontotemporal dementia (FTD) refers to a group of clinical syndromes united by their links to underlying frontotemporal lobar degenera tion (FTLD) pathology. FTD, like the other major neurodegenerative diseases, is considered a disease of abnormal protein aggregation, with either tau or transactive response DNA-binding protein of 43 kDa (TDP-43) implicated in most cases. FTD most often begins in the fifth to seventh decades of life and is nearly as prevalent as Alzheimer’s disease (AD) in this age group. Early studies suggested that FTD may be more common in men than women; however, more recent reports

cast doubt on this finding. Although a family history of dementia is common, autosomal dominant inheritance is seen in only 10–20% of all FTD cases.

■ ■CLINICAL MANIFESTATIONS Familial and sporadic forms of FTLD present with remarkable clinical heterogeneity. Three core clinical syndromes have been described (Fig. 443-1). In the behavioral variant (bvFTD), the most common FTD syn drome, social and emotional dysfunction manifests as apathy, disinhibi tion, compulsivity, loss of empathy, and overeating, often but not always accompanied by deficits in executive control. Two forms of primary progressive aphasia (PPA), the semantic and nonfluent/agrammatic variants, are commonly due to FTLD and are included under the FTD umbrella. In the semantic variant, patients slowly lose the ability to decode word, object, person-specific, and emotion meaning, whereas patients with the nonfluent/agrammatic variant develop profound inability to produce words, often with prominent motor speech impair ment. Any of these three clinical syndromes, but most often bvFTD, may be accompanied by motor neuron disease (MND) (Chap. 448), in which case the term FTD-MND is applied. In addition, the corticobasal syndrome (CBS) and progressive supranuclear palsy–Richardson syn drome (PSP-RS) can be considered part of the FTD clinical spectrum. Furthermore, patients may evolve from any of the major syndromes described above to have prominent features of another syndrome. PART 13 Neurologic Disorders Findings at the bedside are dictated by the anatomic localization of the disorder. Degeneration with atrophy occurs in the medial and orbital frontal cortex and anterior insula in bvFTD; the anterior tem poral region in semantic variant PPA; and the opercular frontal and precentral gyrus of the dominant hemisphere in nonfluent/agrammatic PPA. Typically, parietal functions such as visuospatial processing and arithmetic calculations are unaffected even late in the FTD syndromes. Many patients with nonfluent aphasia or bvFTD later develop aspects of PSP-RS as disease spreads into subcortical or brainstem structures or CBS-like features appear as disease moves into perirolandic cortices. ■ ■GENETIC CONSIDERATIONS Autosomal dominant forms of FTD can result from mutations in C9orf72 (chromosome 9), GRN (chromosome 17), and MAPT (chromosome 17) genes. A hexanucleotide (GGGGCC) expan sion in a noncoding exon of C9ORF72 is the most common genetic cause of familial or sporadic FTD (usually presenting as bvFTD with or without MND) and amyotrophic lateral sclerosis (ALS). The expansion is associated with C9orf72 haploinsufficiency, nuclear mRNA foci con taining transcribed portions of the expansion and other mRNAs, neu ronal

cytoplasmic inclusions containing dipeptide repeat proteins translated from the repeat mRNA, and TDP-43 neuronal cytoplasmic and glial inclusions. The pathogenic significance of these various fea tures is a topic of vigorous investigation. MAPT mutations lead to a change in the alternate splicing of tau or cause loss of function in the FIGURE 443-1 Three major frontotemporal dementia (FTD) clinical syndromes. Coronal magnetic resonance imaging sections from representative patients with behavioral variant FTD (left) and the semantic (center) and nonfluent/ agrammatic (right) variants of primary progressive aphasia (PPA). Areas of early and severe atrophy in each syndrome are highlighted (white arrowheads). The behavioral variant features anterior cingulate and frontoinsular atrophy, spreading to orbital and dorsolateral prefrontal cortex. Semantic variant PPA shows prominent temporopolar atrophy, more often on the left. Nonfluent/agrammatic variant PPA is associated with dominant frontal opercular and dorsal insula degeneration.

tau molecule, thereby altering microtubule binding. With GRN, muta tions in the coding sequence of the gene encoding progranulin protein result in mRNA degradation due to nonsense-mediated decay, leading to a ~50% reduction in circulating progranulin protein levels. Intrigu ingly, homozygous GRN mutations cause neuronal ceroid lipofuscino sis, focusing investigators on the lysosome as a site of molecular dysfunction in GRN-related FTD. Progranulin is a growth factor that binds to tumor necrosis factor (TNF) and sortilin receptors and partici pates in tissue repair and tumor growth. How progranulin mutations lead to FTD remains unknown, but the most likely mechanisms include lysosomal dysfunction and neuroinflammation. Often, MAPT and GRN mutations are associated with parkinsonian features, whereas ALS is rare. Infrequently, mutations in the valosin-containing protein (VCP, chromosome 9), TANK binding kinase 1 (TBK-1), T cell–restricted intracellular antigen-1 (TIA1), and charged multivesicular body protein 2b (CHMP2b, chromosome 3) genes also lead to autoso mal dominant familial FTD. Mutations in the TARDBP (encoding TDP-43) and FUS (encoding fused in sarcoma [FUS]) genes (see below) cause familial ALS, sometimes in association with an FTD syn drome, although a few patients presenting with FTD alone have been reported. ■ ■NEUROPATHOLOGY The pathological hallmark of FTLD is a focal atrophy of frontal, insular, and/or temporal cortex, which can be visualized with neuroimaging studies (Fig. 443-1) and is often profound at autopsy. Neuroimaging studies suggest that atrophy often begins focally in one hemisphere before spreading to anatomically interconnected cortical and subcorti cal regions. Loss of cortical serotonergic innervation is seen in many patients. In contrast to AD, the cholinergic system is relatively spared in FTD, which accounts for the poor efficacy of acetylcholinesterase inhibitors in this group. Although early studies suggested that 15–30% of patients with FTD showed underlying AD at autopsy, progressive refinement in clinical diagnosis has improved prediction accuracy, and most patients diagnosed with FTD at a dementia clinic will show underlying FTLD pathology. Microscopic findings seen across all patients with FTLD include gliosis, microvacuolation, and neuronal loss, but the disease is subtyped according to the protein composition of neuronal and glial inclusions, which contain either tau or TDP-43 in ~90% of patients, with the remaining ~10% showing inclusions containing the FET fam ily of proteins (FUS, Ewing sarcoma protein, TAF-15) (Fig. 443-2). ■ ■PATHOGENESIS In FTLD-tau, the toxicity and spreading capacity of misfolded tau are critical for the pathogenesis of inherited and sporadic tauopathies, although loss of tau microtubule stabilizing function may also play a role. In recent years, the distinctive structures of the misfolded tau in each FTLD tauopathy have been resolved using cryo-electron microscopy, opening up new approaches to diagnosis and treatment. TDP-43 and FET family proteins in contrast, are RNA/DNA binding proteins whose roles in neuronal function are still being actively investigated. TDP-43 is a master regulator of gene expression, and loss of

TDP-43 function results in mis-splicing events leading to mRNA degradation (via nonsense-mediated decay) or aber rant transcripts that give rise to stable but dysfunctional peptides. One key role of TDP-43 and FET family proteins may be the chaperoning of mRNAs to the distal neuron for activity-dependent translation within dendritic spines. Because these proteins also form intra cellular aggregates and produce similar anatomic progression, protein toxicity and spreading may also factor heavily

bvFTD svPPA nfvPPA FTD-MND CBS PSP-RS Frontotemporal lobar degeneration (FTLD) FTLD-tau FTLD-TDP FTLD-FET FTLD-3 CHMP2B Pick's 3R tau CBD 4R tau PSP 4R tau aFTLD-U BIBD Type A (PGRN) (C9ORF72) FTDP-17 MAPT Other: CTE, AGD, MST, GGT Type D VCP FIGURE 443-2 Frontotemporal dementia syndromes are united by underlying frontotemporal lobar degeneration pathology, which can be divided according to the presence of tau, TDP-43, or FUS-containing inclusions in neurons and glia. Correlations between clinical syndromes and major molecular classes are shown with colored shading. Despite improvements in clinical syndromic diagnosis, a small percentage of patients with some frontotemporal dementia syndromes will show Alzheimer's disease neuropathology at autopsy (gray shading). aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CTE, chronic traumatic encephalopathy; FET, FUS, Ewing sarcoma protein, TAF-15 family of proteins; FTD-MND, frontotemporal dementia with motor neuron disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; FUS, fused in sarcoma; GGT, globular glial tauopathy; MST, multisystem tauopathy; nfvPPA, nonfluent/ agrammatic variant primary progressive aphasia; NIBD, neurofilament inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; PSP, progressive supranuclear palsy; PSP-RS, progressive supranuclear palsy–Richardson syndrome; svPPA, semantic variant primary progressive aphasia; Type U, unclassifiable type. in the pathogenesis of FTLD-TDP and FTLD-FET. As with tau, the ultrastructural characteristics of the TDP-43 and FET family protein misfolding events are now being actively characterized, with each pathologically recognized morphological subtype corresponding to a disease-specific fold. Increasingly, misfolded proteins in neurodegenerative disease are recognized as having "prion-like" or "corruptive" properties in that they can template the misfolding of their natively folded (or unfolded) protein counterparts, a process that creates exponential amplification of protein misfolding within a cell and may promote transcellular and even transsynaptic protein propagation between cells. This hypothesis could provide a unifying explanation for the stereotypical and network-rooted patterns of disease spread observed in each syndrome (Chap. 435). Although the term Pick's disease was once used to describe a pro gressive degenerative disorder characterized by selective involvement of the anterior frontal and temporal neocortex and pathologically by intraneuronal cytoplasmic inclusions (Pick bodies), it is now used only in reference to a specific FTLD-tau histopathologic subtype. Classical Pick bodies are argyrophilic, staining positively with the Bielschowsky silver method (but not with the Gallyas method) and also with immunostaining for hyperphosphorylated tau. Recognition of the three FTLD major molecular classes has allowed delineation of distinct FTLD subtypes within each class. These subtypes, based on the morphology and distribution of the neuronal and glial inclusions (Fig. 443-3), account for the vast majority of patients, and some sub types show strong clinical or genetic associations (Fig. 443-2). Despite this progress, clinical features do not allow reliable prediction of the underlying FTLD subtype, or even the major molecular class, for all clinical syndromes. Molecular positron emission tomography (PET) imaging

with ligands chosen to bind misfolded tau protein shows promise, but to date, these ligands only show robust and specific bind ing to AD-related misfolded tau. Because FTLD-tau and FTLD-TDP account for 90% of FTLD patients, the ability to detect pathologic tau (or TDP-43) protein deposition in vivo would greatly improve predic tion accuracy, especially when amyloid PET imaging is negative. ■ ■TREATMENT Caregivers for patients with FTD carry a heavy burden, especially when the illness disrupts core emotional and personality functions of the loved one. Treatment is symptomatic, and there are currently no thera pies known to slow progression or improve symptoms. Many of the

Alzheimer's disease Type B (C9ORF72) Type C CHAPTER 443 NIFID/ NIBD FUS NOS FUS Type U (C9ORF72) (TARDBP) Frontotemporal Dementia behaviors that may accompany FTD, such as depression, hyperorality, compulsions, and irritability, can be ameliorated with antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). Because FTD is often accompanied by parkinsonism, antipsychotics, which can exacerbate this problem, must be used with caution. Experimental therapeutics, most targeting genetic forms of FTD, have just begun to enter clinical trials, but to date, no disease-modifying treatments have shown efficacy. A general approach to the symptomatic management of dementia is presented in Chap. 31. ■ ■PROGRESSIVE SUPRANUCLEAR PALSY SYNDROME PSP-RS is a degenerative disorder that involves the brainstem, basal ganglia, diencephalon, and selected areas of cortex. Clinically, PSPRS begins with falls and executive dysfunction or subtle personality changes (such as mental rigidity, impulsivity, or apathy). Shortly thereafter, a progressive oculomotor syndrome ensues that begins with square wave jerks, followed by slowed saccades (vertical worse than horizontal) before resulting in progressive supranuclear oph thalmoparesis. Dysarthria, dysphagia, and symmetric axial rigidity can be prominent features that emerge at any point in the illness. A stiff, unstable posture with hyperextension of the neck and a slow, jerky, toppling gait are characteristic. Frequent unexplained and sometimes spectacular falls are common secondary to a combination of axial rigidity, inability to look down, and impaired judgment. Even once patients have severely limited voluntary eye movements, they retain oculocephalic reflexes (demonstrated using a vertical doll's head maneuver); thus, the oculomotor disorder is supranuclear. The dementia overlaps with bvFTD, featuring apathy, frontal-executive dysfunction, poor judgment, slowed thought processes, impaired verbal fluency, and difficulty with sequential actions and shifting from one task to another. These features are common at presentation and often precede the motor syndrome. Some patients with a pathologic diagnosis of PSP begin with a nonfluent aphasia or motor speech dis order and progress to classical PSP-RS. Response to l-dopa is limited or absent; no other treatments exist. Death occurs within 5–10 years of onset. Like Pick's disease, increasingly the term PSP is used to refer to a specific histopathologic entity within the FTLD-tau class. In PSP, accu mulation of hyperphosphorylated 4-repeat tau is seen within neurons and glia. Tau neuronal inclusions often appear tangle-like and may be large, spherical ("globose"), and coarse in subcortical and brainstem

A B C PART 13 Neurologic Disorders D E F FIGURE 443-3 Neuropathology in frontotemporal lobar degeneration (FTLD). FTLD-tau (A–C) and FTLD-TDP (D–F) account for >90% of patients with FTLD, and immunohistochemistry reveals characteristic lesions in each of the major histopathologic subtypes within each class: A. Pick bodies in Pick's disease; B. a tufted astrocyte in progressive supranuclear palsy; C. an astrocytic plaque in corticobasal degeneration; D. small compact or crescentic neuronal cytoplasmic inclusions and short, thin neuropil threads in FTLD-TDP, type A; E.

diffuse/granular neuronal cytoplasmic inclusions (with a relative paucity of neuropil threads) in FTLD-TDP, type B; and F. long, tortuous dystrophic neurites in FTLD-TDP, type C. TDP can be seen within the nucleus in neurons lacking inclusions but mislocalizes to the cytoplasm and forms inclusions in FTLD-TDP. Immunostains are 3-repeat tau (A), phospho-tau (B and C), and TDP-43 (D–F). Sections are counterstained with hematoxylin. Scale bar applies to all panels and represents 50 μm in A, B, C, and E and 100 μm in D and F. structures. The most prominent involvement is in the subthalamic nucleus, globus pallidus, substantia nigra, periaqueductal gray, tectum, oculomotor nuclei, pontine nuclei, and dentate nucleus of cerebellum. Neocortical tangle-like inclusions, like those in AD, often take on a more flame-shaped morphology, but the tau folds in AD and PSP are distinct. Prominent tau-positive glial inclusions are an essential feature of PSP. Tufted astrocytes in the neocortex or striatum are the signature lesion (Fig. 443-3). Coiled oligodendroglial inclusions (“coiled bodies”) are common but nonspecific. Most patients with PSP-RS show PSP at autopsy, although small numbers will show another tauopathy (corti cobasal degeneration [CBD] or globular glial tauopathy, or FTLD with a MAPT mutation; Fig. 443-2). In addition to its overlap with FTD and CBS (see below), PSP is often confused with idiopathic Parkinson’s disease (PD). Although elderly patients with PD may have restricted upgaze, they do not develop downgaze paresis or other abnormalities of voluntary eye movements typical of PSP. Dementia ultimately occurs in most patients with PD, often due to the emergence of a full-blown dementia with Lewy bodies (DLB)-like syndrome or comorbid AD-type dementia. Furthermore, the behavioral syndromes seen with DLB differ from PSP (see below). Dementia in PD becomes more likely with increasing age, increasing severity of extrapyramidal signs, long disease duration, and the pres ence of depression. Patients with PD who develop dementia also show cortical atrophy on brain imaging. Neuropathologically, there may be AD-related changes in the cortex or Lewy body disease (LBD)-related α-synuclein inclusions in both the limbic system and cerebral cortex. DLB and PD are discussed in Chaps. 445 and 446, respectively. ■ ■CORTICOBASAL SYNDROME CBS is a slowly progressive dementia-movement disorder associated with severe degeneration in the perirolandic cortex and basal ganglia (substantia nigra and striatopallidum). Patients typically present with asymmetric rigidity, dystonia, myoclonus, and apraxia that render a

progressively incapacitated limb, at times associated with alien limb phenomena in which the limb exhibits unintended motor actions such as grasping, groping, drifting, or undoing. Eventually CBS becomes bilateral and leads to dysarthria, slow gait, action tremor, and a frontalpredominant dementia. Whereas CBS refers to the clinical syndrome, CBD refers to a specific histopathologic FTLD-tau entity (Fig. 443-2). Although CBS was once thought to be pathognomonic for CBD, increasingly it has been recognized that CBS can be due to CBD, PSP, FTLD-TDP, and AD, with the latter accounting for up to 30% of CBS in some series. In CBD, the microscopic features include ballooned, achromatic, tau-positive neurons; astrocytic plaques (Fig. 443-3); and other dystrophic glial tau pathomorphologies that overlap with those seen in PSP. Most specifically, CBD features a severe tauopathy bur den in the subcortical white matter, consisting of axonal threads and oligodendroglial coiled bodies. As shown in Fig. 443-2, patients with bvFTD, nonfluent/agrammatic PPA, and PSP-RS may also show CBD at autopsy, emphasizing the importance of distinguishing clinical and pathologic constructs and terminology. Treatment of CBS remains symptomatic; no disease-modifying therapies are available. ■ ■FURTHER READING Boeve BF et al: Advances and controversies in frontotemporal dementia: Diagnosis, biomarkers, and therapeutic considerations. Lancet Neurol 21:258, 2022. Creekmore BC et al: Neurodegenerative disease tauopathies. Annu Rev Pathol 19:345, 2024. Irwin DJ et al: Frontotemporal lobar degeneration: Defining pheno typic diversity through personalized medicine. Acta Neuropathol 129:469, 2015. Roberson ED: Mouse

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