Chapter 4
Mania

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Abstract Mania is a rare consequence of stroke, and according to the sparse published information, it is difficult to describe its demographic, clinical, and prognostic characteristics. We defined poststroke mania as a mood disorder characterized by an elevated, expansive, or irritable mood, pressured speech, distractibility, grandiosity, hyperactivity, and disinhibition. The diagnosis is based on DSM-IV-TR and Krauthammer and Klerman criteria. A recent systematic review of all cases of poststroke mania allows the collection of 49 studies describing 74 cases. Although there are some cases of mania after left-sided strokes, the majority of cases referred to right-sided lesions. These lesions were more frequently located in the area of orbitofrontal circuit that includes the orbitofrontal cortex, the basotemporal region, the thalamus, and the caudate nucleus. This circuit is crucial for mood regulation and social behavior. The typical patient with mania associated to stroke was a male, without personal/family history of psychiatric disorder, with at least one vascular risk factor, without subcortical atrophy, and with a right cerebral infarct. Similar to primary mania, treatment consists of mood stabilizers and typical or atypical antipsychotics. Mania has high potential disruptive impact after stroke, during the acute care and in the post-acute and rehabilitation phase.

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Definition

Mania is the main symptom for the diagnosis of bipolar disorder, a mood disorder with a prevalence in community studies between 0.4 and 1.6 % and which causes a significant personal and social impairment [1]. Mania is characterized by affective disturbances, such as an elevated, expansive, or irritable mood; changes in speech, with an increased rate or amount; disturbances in language thought and content, with flight of ideas, grandiose ideation, and lack of insight; and behavioral disturbances characterized by overactivity and social disinhibition [1–4]. Primary mania refers to the psychiatric condition itself without a documented brain lesion, and secondary mania describes the manic symptoms caused by neurological, metabolic, or toxic disorders [5]. The term secondary mania was introduced by Krauthammer and Klerman in 1978. Starkstein et al. did not find significant differences between primary and secondary mania clinical profiles [6].

DSM-IV-TR presents the criteria for mood disorder due to a general condition. These criteria should be used for the diagnosis of depression and/or mania after stroke. In Table 4.1, we present the DSM-IV-TR criteria and also the Krauthammer and Klerman criteria for secondary mania.

The literature of mania after stroke is composed predominantly by case reports, small case series, and a few systematic studies. Although mania can be very disrupting during stroke hospitalization and recovery, its low prevalence limits the description of its clinical, demographic, and prognostic features and the identification of

Table 4.1 Diagnostic criteria for poststroke mania

1. DSM-IV-TR diagnostic criteria for 293.83 mood disorder due to stroke with manic features
A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by elevated, expansive, or irritable mood
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a stroke
C. The disturbance is not accounted for by another mental disorder
D. The disturbance does not occur exclusively during the course of a delirium
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
2. Krauthammer and Klerman [5] criteria for secondary mania
A. Symptoms duration of at least 1 week
B. Presence of elevated or irritable mood
C. Presence of at least two of the following symptoms: hyperactivity, pressured speech, flight of ideas, grandiosity, decreased sleep, distractibility, and lack of judgment
D. There was no previous history of manic depressive or other affective illness and symptoms of a confusional state (such as delirium) co-occurring with the mania

evidence-based strategies for dealing with it. Recently, we performed a systematic review of all cases of mania associated with stroke, published until December 2010, aiming to answer to those questions, in order to increase the robustness of the evidence of this neuropsychiatric complication of stroke [7].

We included studies that were required to fulfill the following inclusion criteria: (1) all cases of mania associated with stroke; (2) patients with diagnosis of cerebral infarct (INF), intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH); and (3) adult patients (≥18 years old). From 265 abstracts identified by electronic search, reference lists of the studies collected, and handbooks of neuropsychiatry of stroke, 139 were potentially relevant, of which 49 studies (35 %) met the inclusion criteria. These 49 studies describing 74 cases of poststroke mania were included in the first analysis to determine the most important characteristics of those cases. In a second analysis, from those 49 studies, we selected 32 studies (49 cases), corresponding to cases in whom an explicit temporal and causal relationship between manic symptoms and stroke was documented. The results and conclusions of the systematic review will be discussed throughout this chapter along with data from previous studies and case reports.

Epidemiology

Mania is a rare consequence after stroke and its prevalence seems to be around 1 % [8]. In large community-based studies, such as the Oxfordshire Community Stroke Project and the Perth Community Stroke Study, no cases of poststroke mania were found [9, 10].

In 1922, Babinski first associated a right hemispherical lesion with euphoria, indifference, and anosognosia [11]. Since then, nearly a hundred cases have been described. In our systematic review, we had confirmed the rarity of poststroke mania, identifying only 74 cases of adult stroke patients with mania symptoms published since the 1970s (Table 4.2).

Cohen and Niska described a case of a 59-year-old man, who 2 years after a right temporal hematoma presented manic symptoms, compatible with secondary mania criteria [58]. Jampala and Abrams reported the cases of a 52-year-old man and a 40-year-old man admitted with mania after a left and right hemispherical stroke lesion, respectively [57]. After a review of the cases with mania and the type and location of intracerebral lesions, the authors questioned the association between mania and right lesions. One year later, Cummings and Mendez strengthened the relationship between right hemispheric strokes and mania, while presenting two patients with lesions in the right thalamus, followed by mania [56].

In successive studies, Starkstein et al. collected the highest number of poststroke mania patients. Until 1987, the authors found only three patients with mania among 700 stroke patients [8]. In 1987, they included 11 consecutive patients in a group of secondary mania, four of whom had stroke [6]. The same authors performed a series of studies about mania and depression and collected 17 patients with mania, of whom 9 with a stroke [61].

Table 4.2 Studies ($n=49$) and cases ($n=74$) included in systematic review

	Date	Type of study	Diagnostic criteria	Assessment	Cases	HPPD	HFPD	Laterality
Semiz et al. [12]	2010	Case study	Krauthammer and Klerman	Clinical + scale	1			R
Duggal and Singh [13]	2009	Case study	DSM	Clinical	1	1		L
López et al. [14]	2009	Case study	unknown	Clinical	1			R
Havle et al. [15]	2009	Case study	DSM	Clinical	1			unknown
Rocha et al. [16]	2008	Case study	DSM	Clinical + scale	1		unknown	R
Dervaux and Levasseur [17]	2008	Case study	DSM	Clinical	1			R
Rocha et al. [18]	2008	Case study	DSM	Clinical + scale	1			R
Nagaratnam et al. [19]	2006	Case series	DSM	Clinical	2		unknown	L; R
Goyal et al. [20]	2006	Case study	ICD	Clinical + scale	1		1	R
Mimura et al. [21]	2005	Case study	unknown	Clinical + scale	1	1		R
Celik et al. [22]	2004	Case study	unknown	Clinical + scale	1			R
Huffman and Stern [23]	2003	Case study	unknown	Clinical	1	1	1	R
Gafoor and O'Keane [24]	2003	Case series	unknown	Clinical	1		unknown	R
Colenda [25]	2002	Case study	unknown	Clinical	1		unknown	R
Benke et al. [26]	2002	Case study	unknown	Clinical + scale	1			B
Caeiro et al. [27]	2002	Cohort	DSM	Clinical + scale	1			B
Inzelberg et al. [28]	2001	Case study	DSM	Clinical	1			R
Franco and Chughtai [29]	2000	Case study	unknown	Clinical	1			R
Leibson [30]	2000	Case study	unknown	Clinical + scale	1			R
Fenn and George [31]	1999	Case study	unknown	Clinical	1			L
De León et al. [32]	1999	Case study	unknown	Clinical	1		unknown	R
Börnke et al. [33]	1998	Case study	DSM	Clinical	1			R
Kumar et al. [34]	1997	Case study	ICD	Clinical	1			B
Kulisevsky and Berthier [35]	1997	Case study	DSM	Clinical + scale	1			R
Liu et al. [36]	1996	Case study	DSM	clinical	1			L
Trillet et al. [37]	1995	Case study	unknown	Clinical	1			L

Kulisevsky et al. [38]	1995	Case study	unknown	Clinical + scale	1			R
Tohen et al. [39]	1994	Cohort	unknown	Clinical	7	unknown	unknown	1L; 6?
Kumar and Kuruvilla [40]	1994	Case study	DSM	Clinical	1			R
Berthier and Kulisevsky [41]	1993	Case study	DSM	Clinical + scale	1			R
Turecki et al. [42]	1993	Case study	unknown	Clinical	1			L
Kulisevsky et al. [43]	1993	Case study	DSM	Clinical + scale	1			R
Berthier [44]	1992	Case study	unknown	Clinical + scale	1			R
Starkstein et al. [45]	1991	Cohort	DSM	Clinical + scale	10		unknown	10R
Blackwell [46]	1991	Case study	unknown	Clinical	1	unknown	unknown	R
Fawcett [47]	1991	Case study	unknown	unknown	1	unknown	unknown	R
Snowdon [48]	1991	Retrospective	ICD	unknown	1	unknown		unknown
Drake et al. [49]	1990	Case series	unknown	unknown	2			L; R
Starkstein et al. [50]	1990	Cohort	DSM	Clinical + scale	5			5R
Danel et al. [51]	1989	Case series	unknown	Clinical	1		unknown	R
Mendez [52]	1989	Case series	unknown	Clinical	2	unknown	unknown	L; R
Stone [53]	1989	Retrospective	unknown	unknown	2	unknown	unknown	L; R
Goldschmidt et al. [54]	1988	Case study	unknown	Clinical + scale	1		unknown	B
Bogousslavsky et al. [55]	1988	Case study	unknown	Clinical	1		unknown	R
Cummings and Mendez [56]	1984	Case series	DSM	Clinical	2	1		2R
Jampala and Abrams [57]	1983	Case series	Krauthammer and Klerman	Clinical	2		1	L; R
Cohen and Niska [58]	1980	Case study	Krauthammer and Klerman	Clinical	1			R
Shulman and Post [59]	1980	Retrospective	unknown	unknown	1	unknown	unknown	unknown
Rosenbaum and Barry [60]	1975	Case study	unknown	Clinical	1		unknown	R
					74	4	3	50R, 11L, 4B

Caeiro et al., in a study of neuropsychiatric disturbances in consecutive acute stroke patients, investigated the presence of mania, using the Mania Rating Scale (MRS) [27]. MRS is a widely used mania scale with 11 items, in which mania is operationally defined if patients score at least 12 points [62]. Of the 188 patients, with a mean age of 56.9 and a mean of 6.6 years of education, only one (0.5 %) fulfilled the criteria for mania. This patient presented emotional and behavioral changes characteristic of a manic episode, such as an elevated mood, talkativeness, overactivity, and denial (Case 1).

Celik et al. described a case of a 69-year-old woman with vascular risk factors that after a right temporoparietal stroke had an acute change in her behavior with manic symptoms [22]. Nagaratnam et al. studied two patients with secondary mania following left- and right-sided infarctions [19]. Rocha et al. followed a 47-year-old woman without personal or familiar history of psychiatric disorder and with a right medial frontal lobe, which seems to cause elated mood, irritability, agitation, pressured speech, grandiosity, insomnia, and denial [18].

Mania can manifest in the acute phase but there are reported cases of mania until 2 years after stroke [8]. In fact, the majority of mania cases appeared in the first days after stroke, with 53 % immediately after stroke, 23 % during the first month after stroke, and 23 % after this first month. This delayed presentation may cause difficulties in the identification of manic symptoms.

As stated earlier, the clinical profile of poststroke mania is very similar to the symptom profile of primary mania. We found that the first symptom of mania associated with stroke is the presence of elevated mood, which in some cases alternates with an irritable mood. Other frequent symptoms are an increased rate or amount of speech, insomnia, and agitation. We also counted the number of core symptoms of mania and found that the majority of the patients presented five or more symptoms of mania. The difference between primary and secondary mania seems to be the symptom duration, which is longer in secondary mania probably due to the presence of other comorbidities and the usage of lower doses of antimanic agents.

Risk Factors

Since the first reported cases, the association between poststroke mania and right-sided lesions has been the most quoted risk factor for poststroke mania. Indeed, the majority of patients described in case studies and small case series had right-sided lesions. However, this association has been challenged by the description of cases of mania following left hemispheric lesions [31, 36, 42, 57]. Of the 74 cases of mania and stroke, 50 (68 %) had right-sided lesions, while only 11 (15 %) presented left-sided lesions, a difference which reaches statistical significance (Table 4.3).

With respect to stroke location, almost all cases refer to lesions in the right corticolimbic pathways, an integrated system that includes the limbic system and the

Table 4.3 Description of the 74 cases of stroke and mania

Variables		*N*=74	*p*
Age	<65	35	0.19*
	≥65	22	
	Range (years)	27–91	
	No information	17	
Gender	Female	17	0.00*
	Male	44	
	No information	13	
History of personal psychiatric disorder	Yes	4	0.00*
	No	55	
	No information	15	
Family history of psychiatric disorder	Yes	3	0.00*
	No	38	
	No information	33	
Vascular risk factors	Yes	26	0.00*
	No	7	
	No information	41	
Stroke type	Cerebral Infarct	56	0.00**
	Intracerebral hemorrhage	7	
	Subarachnoid hemorrhage	9	
	No information	2	
Stroke laterality	Right	50	0.00**
	Left	11	
	Bilateral	4	
	No information	9	
Subcortical atrophy	Yes	2	0.00*
	No	36	
	No information	36	
Relation with stroke	Causal and temporal relationship	49	0.00**
	Secondary to treatment	4	
	Previous affective disorder[a]	4	
	Unknown	17	

*Binomial test for proportions; **chi-square test for proportions

[a]Three cases of depression and one case of cyclothymia

basal ganglia. The orbitofrontal circuit is a complex functional network that includes the orbitofrontal cortex, the basotemporal region, the thalamus, and the caudate nucleus. This circuit is crucial for mood regulation and social behavior [6, 19, 26]. Basotemporal and orbitofrontal lesions are frequently associated with mood and behavior changes such as disinhibition, lack of spontaneity and affective control, irritability and aggression, decreased social sensitivity, and confabulation. Secondary mania caused by degenerative, infectious, and traumatic disorders was also frequently related with lesions in basal ganglia [6].

Dysregulation at this level results in decreased prefrontal modulation and mood changes expressed as manic symptoms.

Imaging studies and the systematic review of all the cases evidenced that the majority of patients had large middle cerebral artery infarctions, with lesions in the basal ganglia and frontal and temporal lobes [7]. Blumberg et al. found a decreased activation on the right rostral and orbital prefrontal cortex in patients with mania [63].

Cases of mania with left-sided stroke could be explained by a disconnection between left medial and anterior thalamus with the frontal lobe, which could cause a frontal dysfunction. In this situation the frontal lobes induce an inhibitory effect on the limbic system, which ceases to have its modulating role [24].

Mania could also be related with a biochemical dysfunction caused by right hemisphere stroke, which increases the level of brain serotonin. This mechanism seems to occur in mania caused by antidepressant therapy [13, 45]. Mood-stabilizing drugs seem to be effective in the treatment of manic symptoms due to their effect on serotonin system [18].

Establishing the causal relationship between stroke and mania has also been based on other factors than right-sided lesions, namely, a predisposing genetic factor and/or the presence of subcortical brain atrophy. Starkstein et al. found that stroke patients with mania had more subcortical atrophy than the remaining stroke patients matched by lesion size and location [6]. Krauthammer and Klerman excluded patients with previous affective disorder in the diagnosis of secondary mania [5]. In an epidemiological study about geriatric mania, the authors found that the majority of patients did not have personal or family history of affective disorder [64]. However, in our systematic review, we did not find evidence in favor of these two factors. The majority of poststroke mania cases did not have history of family or personal psychiatric disorder or subcortical atrophy (Table 4.3).

The presence of vascular risk factors, such as hypertension and diabetes, is another factor that characterizes late-onset mania [22, 65]. Fujikawa found a significant association between silent cerebral infarcts and mood disorders in elderly [66]. The desirable control of vascular risk factors has impact not only on the prevalence of stroke and other cardiovascular diseases but also on the prevalence of poststroke consequences, such as mania.

Looking at the range and average age of the poststroke mania cases reported in the literature, we observe that the onset of mania occurs much later in life than that what is characteristic of primary mania. The more recent published exception is a case of mania in a 27-year-old female with a right cerebral infarct and heart surgery 1 year and 6 months before, respectively, and without family or personal history of affective disorder [12]. Cassidy and Carroll suggested a cutoff of 47 years old to distinguish between early-onset and late-onset mania [65].

In the systematic review of poststroke mania, we found that the typical patient with mania associated to stroke was a male, without personal/family history of psychiatric disorder, with at least one vascular risk factor, without subcortical atrophy, and with a right cerebral infarct.

Outcome

The follow-up of these patients was described in a minority of cases. Some patients had recurrent episodes of mania or presented hypomania. We could not confirm that about 30 % of patients may develop a bipolar disorder [61].

Management

The mood, cognitive, and behavioral changes that characterize mania can have a strong impact in stroke management and rehabilitation. In this context, the treatment of manic symptoms should be similar to that which is recommended for primary mania. Treatment consists of mood stabilizers and typical or atypical antipsychotics [13, 18, 67, 68]. These drugs should be prescribed to poststroke mania patients with precautions for three main reasons: older patients have a highly sensitivity to psychotropic drugs, the presence of stroke itself could change their efficacy, and stroke patients had frequently other medical comorbidities [68]. Dosages should be lower and increased slower than in primary mania.

Lithium was frequently used with favorable results, but its use is controversial in cases with cerebral lesions because the stroke itself may alter the sensitivity to lithium neurotoxicity [6, 42, 69]. Anticonvulsant mood stabilizers, such as carbamazepine and valproic acid, were effective in other patients, with the advantage of also preventing poststroke seizures [18]. Antipsychotics were used in cases of severe mania with psychotic symptoms, and in recent years atypical antipsychotics have been preferred because they had comparatively less side effects. Antipsychotics are associated with the emergence of extrapyramidal symptoms and parkinsonian syndromes [25]. Other relevant side effects of neuroleptics include drowsiness, increased risk of falls, prolonged QT interval, cardiac arrhythmias including sudden death, increased risk of cardiovascular events including stroke, decreased threshold for seizures, and weight gain. Benzodiazepines were also used as adjunctive treatment for hyperactivity and insomnia [17].

Different neurotransmitters are involved in the orbitofrontal circuit and their excess seems to mediate the relation between and affective disorder. In addition to serotonin, other neurotransmitters could be involved in poststroke mania, what could explain the diversity of therapeutic response to different substances [19].

In systematic review, we have data on the treatment for only 47 (64 %) of the 74 cases included. Mood stabilizers (lithium, carbamazepine, and valproic acid) were used in 62 %, typical antipsychotics (haloperidol) in 32 %, atypical antipsychotics (olanzapine, risperidone) in 19 %, and benzodiazepines (diazepam, lorazepam) in 13 %. We found three cases of stroke patients with depression that developed mania after antidepressant treatment [33, 36, 42]. Data on dosages, duration of

the treatment, and efficacy were so scarce that it was impossible to provide any meaningful results.

The lack of placebo-controlled and double-blind trials and the marked differences in efficacy between the same or similar drugs in different cases reinforce doubts about the role of pharmacological treatment in the resolution of symptoms and impede the definition of targeted and evidence-based treatment guidelines [6, 17, 68].

Conclusion

Although rare, mania has high potential disruptive impact after stroke, during the acute care and later, in the post-acute and rehabilitation phase. A manic patient has difficulty in understanding why he is in hospital. He resists treatment and rehabilitation strategies, denying and depreciating the disease symptoms. Manic symptoms could be a part of a clinical profile characterized by other neuropsychiatric changes, such as delirium, denial, post-traumatic stress disorder, psychotic disorders, and personality changes due to stroke. We have carefully examined the patient in order to establish the differential diagnosis with these other conditions, because all of them have common symptoms which may mislead the diagnosis. Only a detailed psychiatric/psychological assessment can detect not only the more frequent neuropsychiatric poststroke changes but other rare consequences, such as mania.

Poststroke mania should also be considered in any manic patient who presents concomitant neurological focal deficits and is older than expected for the onset of primary mania. As stressed above, typically these patients are male, without psychiatric antecedents or subcortical atrophy, with vascular risk factors and right infarct.

Case 1: Mania in the Acute Phase of Subarachnoid Hemorrhage

A 65-year-old female, without vascular risk factors and no personal or family history of mood disorders, was admitted because of acute onset of severe headache, vomiting, and brief loss of consciousness. She was alert but somnolent, oriented, and collaborative, with neck stiffness and left hemiparesis (Hunt and Hess' grade 2). CT scan revealed subarachnoid hemorrhage with hematic densities in the basal cisterns, posterior fossa, third and fourth ventricles, and left lateral ventricle, with moderate hydrocephalus (Fig. 4.1). Angiography revealed an intracranial left vertebral artery dissection.

Psychiatric/psychological assessment was performed on the third day of hospitalization. The patient was oriented, but she presented attention and short-term memory mild defects. In the Mania Rating Scale, she presented an elevated mood, with euphoria, elation, and ecstasy (item 1). This period of intense self-satisfaction and optimism alternates with anger (item 9). She

presented a mild overactivity (item 2), a severe increased rate or amount of speech (item 6), and hyper-religiosity (item 8). The patient reported also a decreased need for sleep (item 4) and eating. She admitted a change in his behavior but denied his neurological disease and psychiatric disturbances (item 11), alluding that there was nothing really wrong with her and presenting a carefree, cheerful, and jovial approach to life, with coolness behavior. She scored 12 on Mania Rating Scale. Her behavioral changes were treated with diazepam (5–20 mg). Thirteen days after the first psychiatric assessment, the manic symptoms had regressed, remained only a hyper-religiosity and a decreased need for sleep. The patient was discharge on the 21st day with a modified Rankin Scale score of 1.

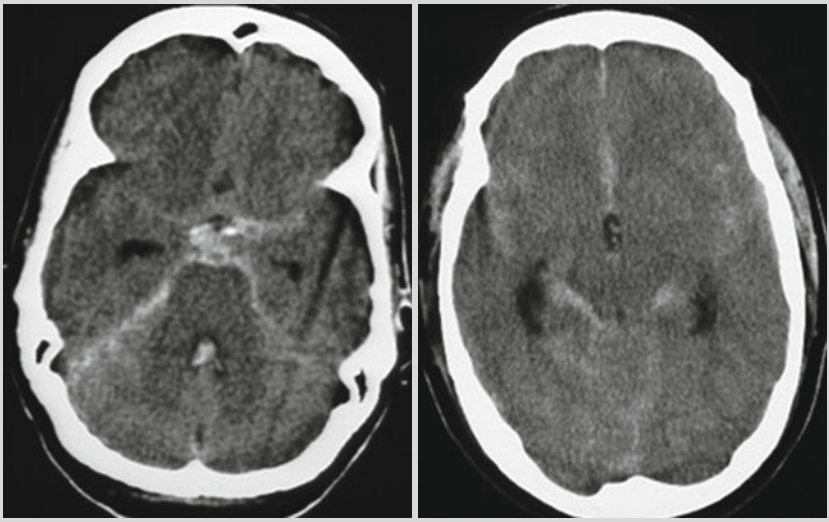

Fig. 4.1 Acute brain CT showing typical features of generalized acute subarachnoid hemorrhage

Case 2: Bipolar Disorder After Stroke

A 68-year-old male, active University Professor, with diabetes, hypertension, and coronary heart disease suffered a minor left hemispheric deep parietal ischemic stroke (Fig. 4.2). He had anomic aphasia, alexia with agraphia, and a slight distal upper limb paresis. No cardiac cause of embolism was detected, and apart from <50 % ipsilateral carotid stenosis, no other abnormal results were found in a comprehensive workup in search of the cause of his stroke. He recovered completely and returned to his previous academic and social

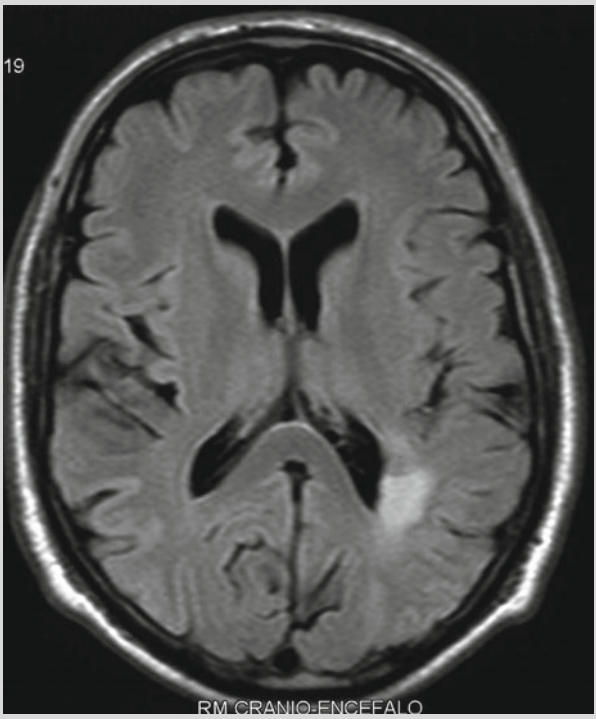

Fig. 4.2 DWI MR showing subcortical left parietal infarct

activities. Two months later he had a fist hypomanic episode characterized by multiple and grandiose plans, optimism, and decreased sleep, which was shortly followed by a prolonged major depressive episode, during which the patient had very depressed mood, pessimism, and decreased energy, avoiding social contacts and staying in bed for prolonged periods. Except for what could be judged retrospectively as a hyperthymic temperament, he had no previous psychiatric history. During the next 2 years, he alternated depressive and manic episodes. Although the patient complained mainly of his depressive symptoms, manic episodes were particularly disturbing because of overactivity, engagement in multiple commitments, decreased sleep, and excessive spending including traveling to foreign countries. Depressive episodes were treated with venlafaxine and manic episodes controlled with haloperidol, although the patient frequently missed medical appointments during these periods. The clinical condition was finally stabilized with lithium and lamotrigine.

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