Mania and Stroke: A Systematic Review

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Key Words

Mania · Stroke

Abstract

Background: 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. **Methods:** We performed a systematic review of all cases of mania and stroke to describe those characteristics. Studies were identified from comprehensive searches of electronic databases, reference lists of the studies collected and handbooks. Two authors independently assessed abstracts, and collected and extracted data. **Results:** From 265 abstracts, 139 were potentially relevant. For the first analysis, which tries to answer the clinical question of the relationship between mania and stroke, 49 studies met the inclusion criteria and described 74 cases. For the second analysis, we looked for an explicit temporal and causal relationship between manic symptoms and stroke, and selected 32 studies describing 49 cases. In both analyses, the typical patient was male, without a personal or family history of psychiatric disorder, with at least one vascular risk factor, but without subcortical atrophy and had suffered a right cerebral infarct. The majority of patients (92%) presented elevated mood as the first symptom. The other frequent symptoms were an increased rate or amount of speech (71%), insomnia (69%) and agitation (63%). **Conclusions:** Post-stroke mania should be

considered in any manic patient who presents concomitant neurological focal deficits and is older than expected for the onset of primary mania. The results of a systematic study of mania in acute stroke with subsequent follow-up and data from diffusion MR or perfusion CT in a multicenter study with a central database would be relevant.

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Introduction

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 behavioural disturbances characterized by overactivity and social disinhibition [1–5]. In 1978, Krauthammer and Klerman [6] introduced the concept of secondary mania for mania caused by neurological, metabolic or toxic disorder.

Mania seems to be a rare consequence of stroke [4, 7–9], but there are few systematic studies of mania in acute stroke [10]. According to previous case reports, post-stroke mania has been related to: (1) predisposing genetic factor, (2) subcortical brain atrophy, and (3) damage to the right corticolimbic pathways [8–16]. Mania seems to be more frequent after right-sided lesions, but there are also reports of mania following left lesions [7, 17,

18]. Based on the sparse published information, it is difficult to describe the demographic, clinical and prognostic characteristics of post-stroke mania. This systematic review of all cases of mania associated with stroke published until December 2010 tries to answer those questions and to increase the robustness of the evidence of this neuropsychiatric complication of stroke.

Methods

Search Strategy

Relevant articles on post-stroke mania cases were identified by electronic search of MEDLINE (until December 2010), by cross-referencing the following MeSH terms: 'bipolar disorder' and 'cerebrovascular disease' (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000327032). We also ran the search in EMBASE and Web of Science databases and identified other cases and studies consulting the reference list of the studies collected and handbooks of neuropsychiatry of stroke. Two authors (C.O.S., J.M.F.) independently assessed all abstracts, and collected and extracted data.

Inclusion Criteria

The primary outcome was the presence of secondary mania after a stroke. For inclusion, studies were required to fulfil the following inclusion criteria: (1) all cases of mania and stroke, (2) patients with a diagnosis of cerebral infarct, intracerebral haemorrhage or subarachnoid haemorrhage, and (3) adult patients (≥ 18 years old).

We performed two different analyses. In the first one, we included all cases of mania and stroke, even when the temporal or causal relationship (Appendix) between them was not explicit or did not exist. This analysis answers the clinical question of what relationship exists between mania and stroke.

In the second analysis, we looked for an explicit temporal and causal relationship between manic symptoms and stroke. Therefore, we applied DSM-IV-TR criteria of mood disorder due to acute stroke with manic features [1] and the criteria of secondary mania by Krauthammer and Klerman [6] (table 1).

Exclusion Criteria

Studies that met one of the following items were excluded from both analyses: (1) duplicate reports; (2) cases with unruptured aneurysms or subdural haematoma, and (3) cases with a diagnosis of bipolar disorder and/or manic episodes before the index stroke.

Data Extraction

The following general descriptive information was extracted from each study: (1) type of study: randomized controlled trial, cohort study, case-control study, case series or case report; (2) diagnosis, diagnostic criteria (DSM or ICD), type of assessment (clinical and/or mania scales) and interviewer (neurologist, psychiatrist, psychologist, nurse); (3) demography and past medical history: age, gender, years of education, personal and/or family history of psychiatric disorder and vascular risk factors; (4) symptoms and signs, onset, duration, description; (5) stroke: type, location and presence of subcortical atrophy on CT/MRI; (6) treat-

Table 1. Diagnostic criteria for post-stroke 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 [6] 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

ment: type and dosage, duration and efficacy of medication, and (7) outcome and follow-up, modified Rankin Scale score and recurrence of manic episodes. To assess the quality of included studies, we analysed data regarding the type of study, quality of assessment and clinical information provided.

Results

Study Identification and Selection

The review flow chart is shown in figure 1. From 265 abstracts, 139 were potentially relevant, of which 49 studies (35%) met the inclusion criteria. These 49 studies describing 74 cases of post-stroke 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 the more restricted criteria of post-stroke mania.

The majority of the studies were case reports (71%) [7, 8, 17, 19–25, 27–30, 32–41, 43–49, 56–58, 60], followed by case series (14%) [16, 18, 26, 31, 51, 53, 54] and cohort studies (8%) [12, 42, 52, 61]. The fact that case reports are usually shorter descriptions explains the lack of information we found when we tried to assess other parameters of the diagnosis and assessment. The cases came predominant-

Fig. 1. Profile of the systematic review.

ly from psychiatric departments (61%), although in many studies it was not explicit if patients were or were not hospitalized and in which department (table 2).

Table 3 shows the reason for the exclusion of 90 of the 139 potentially relevant studies (65%) and their references. We excluded 12 patients from the group of Starkstein and colleagues [9, 10, 13–15, 128] because, although they were cases of stroke and mania, we have only group data.

First Analysis – All Cases of Mania and Stroke

In this first analysis, we included all cases of stroke and mania independently of the causal and temporal relationship between them.

Table 4 shows a summary of the main characteristics of the 74 cases included. Mania cases occurred in young and older stroke patients in a similar proportion ($p = 0.19$). For the other variables, we found significant statistical differences. The typical patient was male, without a personal or family history of psychiatric disorder, with at

least one vascular risk factor, but without subcortical atrophy and had suffered a right cerebral infarct.

In 49 of the 74 cases, we could find a temporal and causal relationship between stroke and mania. In another 4 cases, mania occurred concomitantly with a change or initiation of a treatment which might cause mania in stroke patients with different evolution time periods. Four patients had had a previous affective disorder; 3 had depression [20, 28, 30] and 1 cyclothymia [8]. In 17 cases, we could not determine the relationship between stroke and mania.

Second Analysis – Cases of Secondary Mania

When we only included the 49 patients with post-stroke mania, we found similar results to those obtained in the first analysis (table 5). The typical patient with post-stroke mania was male, without a personal or family history of psychiatric disorder, with at least one vascular risk factor, without subcortical atrophy and had suffered a right cerebral infarct. In all those cases, there

Table 2. Characteristics of included studies

Studies characteristics	Number of studies (n = 49)	References
Type of study		
Randomized controlled trial	0	–
Cohort study	4	12, 42, 52, 61
Case-control study	0	–
Case series	7	16, 18, 26, 31, 51, 53, 54
Case report	35	7, 8, 17, 19–25, 27–30, 32–41, 43–49, 56–58, 60
Retrospective	3	50, 55, 59
Department		
Neurology	14	16, 29, 34, 38–41, 44, 46, 47, 51, 54, 57, 61
Psychiatry	30	7, 8, 12, 17–25, 27, 28, 30–32, 35–37, 42, 43, 45, 48, 50, 52, 55, 58, 59, 60
Both	3	33, 53, 56
Other	1	26
Not specified	1	49
Diagnosis		
DSM criteria	17	12, 16, 17, 20, 22–26, 34, 38, 39, 43, 44, 46, 52, 61
ICD criteria	3	8, 27, 50
Krauthammer and Klerman	3	18, 19, 58
Not specified	26	7, 21, 28–33, 35–37, 40–42, 45, 47–49, 51, 53–57, 59, 60
Type of assessment		
Clinical	27	7, 8, 16–18, 20–22, 24, 26, 30–32, 34, 35, 37, 38, 40, 42, 43, 45, 48, 53, 54, 57, 58, 60
Scale	0	–
Both	17	12, 19, 23, 25, 27, 28, 29, 33, 36, 39, 41, 44, 46, 47, 52, 56, 61
Not specified	5	49–51, 55, 59
Interviewer		
Medical doctor	1	41
Psychiatrist	9	12, 22, 23, 29, 31, 38, 43, 52, 60
Psychologist	1	61
Nurse	0	–
Not specified	38	7, 8, 16–19, 20, 21, 24–28, 30, 32–37, 39, 40, 42, 44–51, 53–59

seemed to be a clear temporal and causal relationship between stroke and mania. 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. In the online supplementary table 2, we present the description of each case.

Table 6 describes the symptoms of mania in those 49 cases. The majority of patients (92%) presented elevated mood as the first symptom. Forty-one percent of patients (n = 20) alternated between elevated and irritable mood and only 8% presented irritability only. The other frequent symptoms were an increased rate or amount of speech (71%), insomnia (69%) and agitation (63%). We counted the number of core symptoms of mania and the majority of patients presented 5 or more symptoms of mania (31% 5–6 symptoms and 27% ≥ 7 symptoms).

Considering the patients for whom we had information, in the majority of these cases mania lasted between 1 and 12 weeks, more frequently without recurrence or minor symptoms (hypomania).

Treatment of Secondary Mania

Of the 74 cases, we have data on the treatment for only 47 cases (64%). 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%. Data on dosages, duration of the treatment and efficacy were so scarce that it was impossible to provide any meaningful results.

Table 3. Excluded studies

Criteria	Description	Number of studies (n = 90)	References
Duplicated reports	Revisions Description of not new cases	32 (36%)	9–11, 13–15, 62, 64, 68–71, 78, 80, 88, 93, 98, 99, 101–104, 107, 109, 110, 112, 114, 117, 125, 128, 132, 137
No stroke	Aneurisms unruptured Subdural haematoma No stroke	19 (21%)	63, 65, 72, 73, 77, 79, 81, 84, 86, 100, 106, 121, 124, 126, 130, 131, 133, 135, 142
Previous affective disorder	Bipolar disorder Mania Other neuropsychiatric disturbances	32 (36%)	5, 66, 67, 74–76, 82, 83, 85, 87, 89, 91, 92, 94, 95, 97, 105, 108, 113, 115, 116, 118, 120, 122, 123, 127, 129, 134, 136, 138, 140, 141
Studies not found	Articles not available and contact with authors impossible	7 (7%)	90, 96, 111, 119, 139, 143, 144

Discussion

This systematic review confirms the rarity of post-stroke mania because in about 50 years we found only 74 reported cases of adult stroke patients with mania symptoms. Robinson et al. [10] and Dunne et al. [145] identified only 3 cases of post-stroke mania in a series of 700 and 661 consecutive stroke patients, respectively. Among 188 consecutive acute stroke patients, our group found 3 (1.6%) cases of mania [61]. Although mania can be very disrupting during hospitalization and recovery, its low prevalence limits the description of clinical, demographic and prognostic features and the identification of evidence-based strategies for dealing with it.

We found a typical patient to be male, without a personal/family history of psychiatric disorder, with at least one vascular risk factor, without subcortical atrophy and with a right cerebral infarct. Our results support previous research which concludes that there is a significant relationship between post-stroke mania and right hemispheric lesions causing a dysfunction in the ventral limbic circuit that involves the right orbitofrontal and basotemporal cortices, dorsomedial thalamic nucleus and head of the caudate nucleus [10, 16, 27, 78, 80]. The orbitofrontal circuit is a complex functional network that includes the orbitofrontal cortex, the basotemporal region, the thalamus and the caudate nucleus and is a central circuit in mood regulation and social behaviour [16, 33].

Establishing a causal relationship between stroke and mania has also been based on other factors than right lesions. The lack of a previous personal or family psychiatric affective disorder, the presence of vascular risk factors and

a temporal relationship between the vascular event and the mood change in the absence of other potential precipitants of mania reinforce this etiological relationship [29, 30]. Also, if we look at the age range and average age of the included cases, we see that the onset of mania occurs much later in life than what is characteristic of primary mania.

Robinson and colleagues [10, 15] suggested that mania was associated with a genetic predisposition and/or subcortical atrophy. This was not supported by the present systematic review because in the majority of post-stroke mania cases we did not find a family or personal history of psychiatric disorder or subcortical atrophy. Krauthammer and Klerman [6] excluded patients with previous affective disorder in the diagnosis of secondary mania. In an epidemiological study about geriatric mania, the authors found that the majority of patients did not have a personal or family history of affective disorder [146]. We could not detect a significant role of subcortical atrophy.

The temporal relationship between stroke and mania ranged from immediately after stroke to up to 2 years thereafter [14].

The clinical profile of post-stroke mania is very similar to primary mania, characterized mainly by elevated mood/euphoria, pressured speech, flight of ideas, grandiosity and insomnia [9, 16, 17, 30, 46, 57]. Starkstein et al. [15] did not find significant differences in the frequency of these symptoms in secondary and primary mania patients.

The follow-up of these patients was described in a minority of cases and some of these had recurrence of mania or presented hypomania. We could not confirm that about 30% of patients may develop a bipolar disorder [10].

Table 4. Description of the 74 cases of stroke and mania

Variables	Cases (n = 63)	p
Age		
<65	35	0.19 ^a
≥65	22	
Range	27–91	
No information	17	
Gender		
Female	17	0.00 ^a
Male	44	
No information	13	
History of personal psychiatric disorder		
Yes	4	0.00 ^a
No	55	
No information	15	
Family history of psychiatric disorder		
Yes	3	0.00 ^a
No	38	
No information	33	
Vascular risk factors		
Yes	26	0.00 ^a
No	7	
No information	41	
Stroke type		
Cerebral infarct	56	0.00 ^b
Intracerebral haemorrhage	7	
Subarachnoid haemorrhage	9	
No information	2	
Stroke laterality		
Right	50	0.00 ^b
Left	11	
Bilateral	4	
No information	9	
Subcortical atrophy		
Yes	2	0.00 ^a
No	36	
No information	36	
Relation with stroke		
Causal and temporal relationship	49	0.00 ^b
Secondary to treatment	4	
Previous affective disorder ^c	4	
Unknown	17	

^a Binomial test for proportions.^b χ^2 test for proportions.^c Three cases of depression and one case of cyclothymia.

A variety of psychotropic drugs have been used to treat post-stroke mania, mainly mood stabilizers, typical antipsychotics and atypical antipsychotics with variable outcome [11, 27, 30, 78]. Lithium was frequently used with favourable results, but its use is controversial in cases with

Table 5. Description of the 49 cases of stroke and mania

Variables	Cases (n = 45)	p
Age		
<65	25	0.05 ^a
≥65	11	
Range	27–81	
No information	13	
Gender		
Female	11	0.01 ^a
Male	28	
No information	10	
History of personal psychiatric disorder		
Yes	1	0.00 ^a
No	47	
No information	1	
Family history of psychiatric disorder		
Yes	2	0.00 ^a
No	29	
No information	18	
Vascular risk factors		
Yes	20	0.02 ^a
No	7	
No information	22	
Stroke type		
Cerebral infarct	36	0.00 ^b
Intracerebral haemorrhage	6	
Subarachnoid haemorrhage	7	
No information	0	
Stroke laterality		
Right	39	0.00 ^b
Left	7	
Bilateral	3	
No information	0	
Subcortical atrophy		
Yes	0	0.00 ^a
No	29	
No information	20	

^a Binomial test for proportions.^b χ^2 test for proportions.

cerebral lesions [16, 60]. Antipsychotics were used in cases of severe mania with psychotic symptoms, and throughout all these years atypical antipsychotics have been preferred because they have comparatively minor side effects. Benzodiazepines were also used as adjunctive treatment for hyperactivity and insomnia [32]. These drugs should be given to post-stroke mania patients with caution for two main reasons: first because older patients have a high sensitivity to psychotropic drugs and second because the presence of stroke itself could change their efficacy [114].

Table 6. Symptoms of mania in 49 cases of stroke and mania

Ref.	Elation	Irritability	Hyperactivity	Talkativeness	Distractibility	Flight of ideas	Grandiosity	Sleeplessness	Denial	Symptoms, n	Duration weeks	Follow-up	Recurrence
19	x						x	x		3	12		
24	x	x	x		x	x		x	x	7			
25	x	x	x	x	x		x	x	x	8	8	y	n
26	x	x	x	x		x		x		6		y	hypomania
26	x	x	x	x				x	x	6			
27	x	x	x	x	x				x	6	12	y	n
29	x		x	x		x	x	x		6	4	y	hypomania
31	x	x	x	x				x	x	6			
32	x	x	x	x	x	x	x	x	x	9			
33	x		x	x	x	x		x	x	7	8	y	hypomania
34	x		x	x	x	x		x	x	7	8		
36	x			x					x	3	10	y	y
7	x	x	x	x	x	x		x		7	8	y	n
38	x	x	x	x		x	x	x	x	8			
17	x	x	x	x		x	x	x		7	8		
40	x			x				x		3	8		n
41	x		x	x				x		4	4		
43	x	x	x	x		x	x			6	38		
45	x	x	x	x			x	x		6			
46	x			x	x	x	x	x	x	7	4-8	y	n
47	x	x	x	x	x	x				6	52		
48	x	x	x	x	x	x		x		7	cyclic	y	n
12	x							x					
12	x							x					
12	x							x					
12	x							x					
12	x							x					
12	x												
12	x												
12	x												
12	x												
51		x	x				x	x		4		y	n
51		x	x				x	x		4		y	n
52	x		x	x	x		x	x		6			
52	x		x	x		x	x	x		6		y	y
52	x			x			x			3			
52	x			x			x			3			
52	x			x			x			3			
53		x	x	x				x		4	cyclic		
56	x	x	x	x		x	x			6		y	y
57	x			x		x				3	8	y	n
16	x	x	x	x				x	x	6	4		n
16	x	x	x	x		x		x	x	7	6	y	y
18	x	x	x	x		x	x	x		7			
18		x	x	x	x	x				5			
58	x	x	x	x		x		x		6	cyclic	y	y
60	x		x	x			x		x	5	cyclic	y	y
61	x	x	x	x	x	x	x	x	x	9	2	y	n
Total	45	24	31	35	13	21	20	34	15			18	9

The lack of placebo-controlled and double-blind trials and the differences in efficacy between the same or similar drugs in different cases reinforces doubts about the role of pharmacological treatment and impedes the definition of targeted and evidence-based treatment guidelines [2, 16, 32, 114].

This systematic review had some limitations caused essentially by the nature of the studies. Case studies and case series are shorter reports and the authors referred only to what they considered to be the more relevant data about the case. So, we have a significant proportion of missing data on important variables. In many cases, we did not know if the missing information was not assessed or if it was only omitted. We have reviewed reports since 1960, and over the years the definition of what could be important to assess and report has changed. The assessment methods, psychological tests and imagiological techniques improved markedly over time. Case reports also vary in many variables, such as diagnostic criteria, methods of assessment, treatment and follow-up. Moreover, we cannot exclude that there were other cases not published that were presented at congresses and other meetings and even others that were underdiagnosed in the context of a sudden and serious disease such as stroke, specially in cases with major symptoms like aphasia. Finally, a publication bias could exist favouring the dissemination of positive cases and not others. Moreover, since right-sided lesion cases have been published, more attention may have been devoted to the presence and diagnosis of manic symptoms in these patients.

In conclusion, post-stroke mania should be considered in any manic patient who presents concomitant neurological focal deficits and is older than expected for the onset of primary mania. More frequently, these patients were male, without psychiatric antecedents or subcortical atrophy, with vascular risk factors and right infarct. Although rare, the results of a systematic study of mania in acute stroke with follow-up and data from diffusion MR or perfusion CT in a multicenter study with a central database would be relevant.

Appendix

Temporal or causal relationship = there is evidence from historical data, physical examination, or laboratory findings that manic symptoms are a direct physiological consequence of a stroke, occurring immediately or up to 3 years thereafter.

History of personal psychiatric disorder = previous psychiatric disorder was diagnosed if the patient had at least once in his/her lifetime been treated for a psychiatric disorder and specific medication for this condition had been prescribed for more than a month.

Family history of psychiatric disorder = presence of psychiatric disorder diagnosed in family relatives.

Vascular risk factors = includes hypertension, diabetes mellitus, hyperlipidaemias, myocardial infarction, angina pectoris, heart failure, atrial fibrillation, lower limb arteriopathy and peripheral vascular disease, history of stroke and/or transient ischaemic attack; cigarette smoking and alcohol consumption.

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